

Pharmacological and Psychosocial Treatments in Schizophrenia

SECOND EDITION



Edited by **David J Castle, David L Copolov,**
Til Wykes and Kim T Mueser

informa
healthcare



JANSSEN-CILAG

Pharmacological and Psychosocial Treatments in Schizophrenia

Second Edition – Revised, expanded and fully updated

Edited by

David J Castle MSc DLSHTM MD MRCPsych FRANZCP

Chair of Psychiatry

St Vincent's Health and The University of Melbourne

Fitzroy, Victoria, Australia

David L Copolov PhD FRACP FRANZCP

Professor of Psychiatry

Monash University

Clayton, Victoria, Australia

Til Wykes MPhil PhD

Professor and Head, Centre for Recovery in Severe Psychosis

Institute of Psychiatry, London, UK

Kim T Mueser PhD

Professor of Psychiatry

Dartmouth Medical School

Hanover, NH, USA

informa
healthcare

© 2008 Informa UK Ltd

First published in the United Kingdom in 2003

Second edition published in the United Kingdom in 2008 by Informa Healthcare, Telephone House, 69–77 Paul Street, London EC2A 4LQ. Informa Healthcare is a trading division of Informa UK Ltd. Registered Office: 37/41 Mortimer Street, London W1T 3JH. Registered in England and Wales number 1072954

Tel: +44 (0)20 7017 5000

Fax: +44 (0)20 7017 6699

Website: www.informahealthcare.com

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of the publisher or in accordance with the provisions of the Copyright, Designs and Patents Act 1988 or under the terms of any licence permitting limited copying issued by the Copyright Licensing Agency, 90 Tottenham Court Road, London W1P 0LP.

Although every effort has been made to ensure that all owners of copyright material have been acknowledged in this publication, we would be glad to acknowledge in subsequent reprints or editions any omissions brought to our attention.

Although every effort has been made to ensure that drug doses and other information are presented accurately in this publication, the ultimate responsibility rests with the prescribing physician. Neither the publishers nor the authors can be held responsible for errors or for any consequences arising from the use of information contained herein. For detailed prescribing information or instructions on the use of any product or procedure discussed herein, please consult the prescribing information or instructional material issued by the manufacturer.

A CIP record for this book is available from the British Library.

Library of Congress Cataloging-in-Publication Data

Data available on application

ISBN-10: 0 415 42156 X

ISBN-13: 978 0 415 42156 0

Distributed in North and South America by

Taylor & Francis

6000 Broken Sound Parkway, NW, (Suite 300) Boca Raton, FL 33487, USA

Within Continental USA

Tel: 1 (800) 272 7737; Fax: 1 (800) 374 3401

Outside Continental USA

Tel: (561) 994 0555; Fax: (561) 361 6018

Email: orders@crcpress.com

Distributed in the rest of the world by

Thomson Publishing Services

Cheriton House

North Way

Andover, Hampshire SP10 5BE, UK

Tel: +44 (0)1264 332424

Email: tps.tandfsalesorder@thomson.com

Composition by Cepha Imaging Pvt. Ltd, Bangalore, India

Printed and bound in India by Replika Press Pvt. Ltd

Front cover artwork by Andrew Galt © UK 2008

Contents

List of contributors	v
Foreword to the first edition	vii
Foreword to the second edition	ix
Acknowledgments	xi
1. Psychopharmacological management of schizophrenia <i>David J Castle, Nga Tran, and Deirdre Alderton</i>	1
2. Psychological approaches to the management of persistent delusions and hallucinations <i>Til Wykes, Gina Smith, and Craig Steel</i>	23
3. Management of negative symptoms <i>David L Copolov and David J Castle</i>	35
4. Cognitive dysfunction in schizophrenia <i>Til Wykes and David J Castle</i>	47
5. Depression and anxiety in schizophrenia <i>David J Castle, Til Wykes, and Natalie Knoesen</i>	61
6. General health of people with schizophrenia <i>Urban Ösby, Peter Fahnstock, and John W Newcomer</i>	81
7. Substance abuse comorbidity in schizophrenia <i>Wynne James, Kim Mueser, and David J Castle</i>	99

8. Management of acute behavioral disturbance in psychosis <i>David J Castle, Nga Tran, and Deirdre Alderton</i>	111
9. Managing the violent behaviors associated with the schizophrenic syndrome <i>Paul E Mullen and Danny H Sullivan</i>	129
10. Understanding and enhancing adherence to treatment in people with schizophrenia <i>Peter Hayward and Til Wykes</i>	143
11. Psychological interventions to help people with psychiatric disabilities succeed at work <i>Morris D Bell and Jimmy Choi</i>	151
12. Enhancing socialization capacities in people with schizophrenia <i>Shirley M Glynn and Anna Lui</i>	165
13. Clinical needs of women with schizophrenia <i>Paul B Fitzgerald and Mary V Seeman</i>	179
14. Family intervention in schizophrenia <i>Christine Barrowclough and Til Wykes</i>	193
15. A treatment approach to the patient with first-episode schizophrenia <i>Richard Drake and Shôn Lewis</i>	205
16. Treatment-resistant schizophrenia <i>William D Spaulding, Robert W Johnson, Jeffrey R Nolting, and Amanda Collins</i>	221
17. Rating scales in schizophrenia: clinical applicability <i>Marc Corbière and Tania Lecomte</i>	237
Index	253

Contributors

Deirdre Alderton

Clinical Pharmacist
Fremantle Hospital, South Metropolitan
Health Region
Australia

Christine Barrowclough BA MSc PhD

Professor, University of Manchester
Manchester, UK

Morris D Bell PhD

VA Connecticut Healthcare System and
Yale University School of Medicine
West Haven, CT, USA

David J Castle MSc DLSHTM MD MRCPsych
FRANZCP

Chair of Psychiatry
St Vincent's Health and The University of
Melbourne
Fitzroy, Victoria, Australia

Jimmy Choi

VA Connecticut Healthcare
System and Yale University
School of Medicine
West Haven, CT, USA

Amanda Collins

University of Nebraska
Lincoln, NE, USA

David L Copolov PhD FRACP FRANZCP

Professor of Psychiatry
Monash University
Clayton, Victoria, Australia

Marc Corbière PhD

Assistant Professor, Department of
Rehabilitation
University of Sherbrooke
and
Researcher, Centre for Action in Work
Disability Prevention and Rehabilitation
Montreal, Quebec, Canada

Richard Drake MRCPsych PhD

Senior Lecturer in Adult Psychiatry University
of Manchester
Manchester, UK

Peter Fahnestock MD

Instructor, Department of Psychiatry
Washington University
School of Medicine
St Louis, MO, USA

Paul B Fitzgerald MBBS MPM PhD FRANZCP

Alfred Psychiatry Research Centre, The Alfred
Hospital and Monash University School of
Psychology, Psychiatry and Psychological
Medicine
Victoria, Australia

Shirley M Glynn PhD

Department of Psychiatry and Biobehavioral
Sciences and Semel Institute of Neuroscience
and Human Behavior
University of California
Los Angeles, CA, USA

Peter Hayward PhD

Consultant Clinical Psychologist Institute of
Psychiatry
King's College London
London, UK

Wynne James

Drug and Alcohol Office
Government of Western Australia
Perth, WA, Australia

Robert W Johnson

University of Nebraska
Lincoln, NE, USA

vi List of contributors

Natalie Knoesen PhD
Research Coordinator,
St Vincent's Mental Health
St Vincent's Hospital
Melbourne, VIC, Australia

Tania Lecomte PhD
Assistant Professor, Department of Psychology
University of Montreal
and
Researcher, Fernand Seguin Research Centre
Montreal, Quebec, Canada

Shôn Lewis FRCPsych MD
Professor of Adult Psychiatry University of
Manchester
Manchester, UK

Anna Lui MSW
Department of Social Welfare School of
Public Affairs
University of California
Los Angeles, CA, USA

Kim T Mueser PhD
Professor of Psychiatry
Dartmouth Medical School
Hanover, NH, USA

Paul E Mullen MB BS DSc FRANZCP FRC Psych
Professor of Forensic Psychiatry
Monash University
and
Clinical Director, Victorian Institute of
Forensic Mental Health
Thomas Embling Hospital
Fairfield, Australia

John W Newcomer MD
Professor of Psychiatry, Psychology and
Medicine
Washington University School of Medicine
St Louis, MO, USA

Jeffrey R Nolting
University of Nebraska
Lincoln, NE, USA

Urban Ösby MD PhD
Assistant Professor in Psychiatry
Karolinska Institute
and
Senior Consultant in Psychiatry
Psychiatry Northeast
Stockholm, Sweden

Mary V Seeman MD
Professor Emeritus
University of Toronto
Department of Psychiatry
Institute of Medical Science
Toronto, ON, Canada

Gina Smith
Research Worker
Institute of Psychiatry
London, UK

William D Spaulding PhD
Professor of Psychology
University of Nebraska
Lincoln, NE, USA

Craig Steel
Lecturer in Psychology
Institute of Psychiatry
London, UK

Danny H Sullivan MBBS MBioeth MHlthMedLaw
MRCPsych FRANZCP
Consultant Psychiatrist
Assistant Clinical Director
Victorian Institute of Forensic Mental Health
Melbourne
and
Honorary Lecturer, Department of
Psychological Medicine
Monash University
Clayton, Victoria, Australia

Nga Tran BPharm
Clinical Pharmacist, St Vincent's
Mental Health
St Vincent's Hospital
Melbourne, VIC, Australia

Til Wykes MPhil PhD
Professor and Head, Centre for Recovery in
Severe Psychosis
Institute of Psychiatry, London, UK



Foreword to the First Edition

Treating patients with severe and persistent mental illnesses such as schizophrenia is not for the faint of heart. There are many reasons for this cautionary view including the fact that these illnesses are severe, recurrent, debilitating, and often, if not usually, lifelong. They are also poorly understood by scientists in terms of their etiology and pathophysiology, by lay persons in terms of their level of recognition and understanding of the symptoms and nature of mental illness, and by most clinicians with the exception of those who are trained and experienced in their care and management. Moreover, the patients themselves often lack awareness of their illness and are either not motivated or deny the need for treatment.

Despite these numerous and significant obstacles, the body of knowledge and repertoire of therapeutic modalities for the treatment of schizophrenia is prodigious. This is fortuitous as patients with schizophrenia suffer from multiple kinds of morbidity and disabilities, and thus often need different treatments. Patients experience a spectrum of symptoms including psychosis (positive symptoms), and disturbances in drive, interest, affect, and impoverishment of thought and speech (collectively known as negative symptoms) and also may incur mood symptoms of depression, anxiety, or excitement. In addition, at some point in the course of their illness, they sustain impairments in their cognition and functional capacity. They also exhibit disproportionately high rates of suicide, substance abuse, and violent or aggressive behaviors. Finally, the impact of the illness is not limited to the patients themselves. The consequences of the illness have devastating effects on the family and ultimately on the community at large

which all too frequently is required to assume some level of responsibility for persons with mental illness.

The revised edition of *Pharmacological and Psychosocial Treatments in Schizophrenia* edited by David Castle, David Copolov, and Til Wykes provides a thoughtful, comprehensive, and state of the art guide for the clinical management of patients with severe and persistent mental illness. It is clear to anyone who works with such patients that although medication is an essential component of treatment, by itself it is insufficient. Thus, this well conceived volume begins with psychopharmacological management but then immediately proceeds to discuss methods for the psychological management of psychosis before considering other pathological dimensions of the illness (management of negative symptoms, cognitive dysfunction in schizophrenia, depression and anxiety in schizophrenia), and clinical complications of the illness (substance abuse comorbidity in schizophrenia; management of acute arousal in schizophrenia). The final three chapters address the prevalent and challenging problems of promoting adherence to treatment, work, and recovery and family intervention in schizophrenia.

The beauty of this work lies in its pragmatic and fundamental selection of topics and their natural combination in this concise, lucid, and straightforward volume. The seemingly effortless composition of this book makes the integration of pharmacological and psychosocial therapies appear seamless and natural. Would that this were the case in mental health-care systems and general clinical practice. Regrettably this is the exception with limited and fragmentary therapeutic services being the rule of what usually exists in mental health-care settings. To paraphrase the divine plea 'from your mouth to God's ears', one might say that for comprehensive and integrated treatment for patients with severe and persistent mental illness 'from the mouths of Castle, Copolov and Wykes to the ears of all mental health-care providers'.

Jeffrey A Lieberman MD
University of North Carolina School of Medicine
Chapel Hill, North Carolina
USA



Foreword to the Second Edition

It has been a welcomed trend in recent years to see the emergence of specialist books on schizophrenia. This condition is so complex and, although major treatment breakthroughs are still elusive, the field is moving at a pace that is hard for the specialist – let alone the busy general psychiatrist – to keep up with treatment developments. In a relatively short time, there has been a shift in treatment focus with growing emphasis now on psychiatric and medical comorbidities, and on improving functionality. Additionally, there is greater need to define and measure these outcomes, whether these relate to risky behaviors or more generally to broader functional outcomes of work performance and socialization.

Accordingly, I was delighted to see the next version of this book. The second edition of *Pharmacological and Psychological Treatments in Schizophrenia* will serve as an authoritative source on schizophrenia for mental health clinicians, particularly since it has been updated to include new chapters directly pertinent to the most current issues in schizophrenia research and therapeutics.

The latest text reflects advances in both pharmacological and psychosocial treatments of schizophrenia. From lifestyle issues to clinical rating scales, and even to the delivery of care for females with schizophrenia, the textbook covers the clinical essentials of schizophrenia in a balanced and remarkably comprehensive manner. As a departmental chairman, I am particularly pleased to see that every effort has been made to include the very latest key publications while also citing references to seminal papers on schizophrenia

in the chapters. Given the scope of this text, this balance is no small task and the editors (Drs Castle, Copolov, Wykes, and Mueser) and contributing authors are to be congratulated.

Recognized experts, with the guidance and oversight of the editors, have contributed clinically relevant chapters. It is evident that each contributor has carefully ensured that his or her chapter is complete and the editors have been careful in their role of delivering a well-integrated textbook. This is exemplified best in the chapters on cognitive dysfunction in schizophrenia (Chapter 4) and enhancing socialization (Chapter 12), although this approach is evident throughout the text.

While my own research focus is on the medication treatment of schizophrenia, I was very pleased to see excellent contributions on facets of vocational and social impairments of this illness as well as the emphasis on psychiatric and medical comorbidities. These are practical and contain clinically pertinent new material. The textbook is well weighted with respect to psychological and somatic therapies, a key consideration for trainees. Having two chapters dedicated to acute agitation and then violence and the forensic aspects of schizophrenia makes a lot of sense since this is such an important and complex focus in management today. As a point of observation, the reader may also wish to keep an eye on emerging medication augmentation studies for refractory schizophrenia. This is covered briefly in the chapter on treatment-resistant schizophrenia and is always an area of innovation (even if the evidence base is weakly confined to mainly small clinical trials). A chapter on recovery and consumerism should make its way into the third edition, though that may be some time off as this version is so current that it will likely have a substantial 'shelf-life'.

Drs Castle, Copolov, Wykes, and Mueser, and contributing authors have done an excellent job in providing a comprehensive clinically pertinent text that hopefully with wide distribution will raise understanding of the modern-day treatment of schizophrenia.

Peter F Buckley MD
Department of Psychiatry
Medical College of Georgia
Augusta, GA, USA



Acknowledgments

A number of individuals gave helpful advice regarding various chapters of this book, at varying stages of production. We thank these people, who include Shon Lewis (Manchester, UK), Peter Norrie (ACT, Australia), Josh Geffen (Brisbane, Australia), Dan Lubman (Melbourne, Australia), Allan White (Newcastle, Australia), Christine Culhane (Melbourne, Australia), John Farhall (Melbourne, Australia), Julie Lord (Melbourne, Australia) and John Fielding (Melbourne, Australia). For administrative support, we thank, in particular Malinda Edwards. Professor Castle acknowledges with thanks the support of the Baker Foundation.

Psychopharmacological management of schizophrenia

David J Castle, Nga Tran, and Deirdre Alderton

It is now well established that antipsychotic medications are one of the mainstays of treatment for psychotic disorders. This has been shown to be the case for both acute management and maintenance treatment aimed at reducing relapse¹. This chapter concentrates on the pharmacological aspects of the initial and ongoing treatment of psychosis (the management of acute behavioral disturbance in psychosis is covered in Chapter 8).

Historical background

The discovery of the calming effects of chlorpromazine in the 1950s set the modern pharmacological management of psychotic disorders in motion. Further antipsychotics were soon developed, based on the notion that it was the dopamine D2 blockade in the brain that mediated the antipsychotic effects. Haloperidol was the 'cleanest' D2 blocker of all these earlier agents and became the benchmark against which other agents were measured.

One of the drawbacks of the older, so-called typical antipsychotics is their greater propensity to produce extrapyramidal side-effects (EPSE) such as parkinsonism, dystonias, and akathisia, and the longer-term problem of tardive dyskinesia (TD)² (Table 1.1). It was thus with great interest that the atypical antipsychotic clozapine was welcomed to the marketplace in the mid-1960s. Clozapine was noted to be a potent antipsychotic with minimal propensity to produce EPSE/TD and particular efficacy in so-called treatment-resistant cases. However, the limitations of clozapine, notably its propensity to cause a potentially fatal agranulocytosis in around 1% of patients, led to its

Table 1.1 Extrapyramidal side-effects (EPSE) of antipsychotic drugs

<i>Type of EPSE</i>	<i>Clinical features</i>
Parkinsonism	Mask-like facies Muscle rigidity ('cog-wheeling') 'Pill-rolling' tremor Shuffling gait, 'festination', retropulsion Diminished arm swing
Dystonia	Acute Involuntary sustained spasm of muscles, notably head and neck (e.g. facial grimacing, protrusion of tongue, opisthotonos, oculogyric crisis); may be painful Chronic Sustained involuntary spasm of skeletal muscles, resulting in abnormal posture (e.g. trunk)
Akathisia	Subjective: feeling of 'inner restlessness', with a drive to move Objective: frequent changes of posture, inability to sit still, constant walking
Tardive dyskinesia	Orobuccofaciolingual: abnormal involuntary movements of face, tongue, and lips with chewing movements, tongue movement, puckering of lips, grimacing May be associated truncal movements, and choreoathetoid movements of the extremities

withdrawal in a number of countries in the 1970s (it was reintroduced in the late 1980s, with strict hematological monitoring controls), and the race was on to develop clozapine-like drugs that did not cause blood dyscrasias.

Based on the belief that the atypicality of clozapine was consequent upon its high ratio of serotonin (5HT₂):dopamine D2 receptor occupancy, the pharmaceutical industry produced risperidone, which mimicked that particular pharmacological property of clozapine. This product was the first novel atypical antipsychotic to be marketed, and showed a relatively benign side-effect profile compared with haloperidol, though EPSE still occurred at higher doses³. Subsequent novel atypicals include olanzapine, quetiapine, zotepine, sertindole, ziprasidone, and amisulpride. More recently, the partial D2 agonist aripiprazole has been added to the clinical armamentarium. Aripiprazole is a novel antipsychotic with a unique combination of dopamine and serotonin receptor binding affinities and activities. It has been suggested that aripiprazole's partial agonist activity at dopamine D2 receptors stabilizes

the dopamine system while avoiding the hypodopaminergia that may limit the tolerability of currently available antipsychotics.

Paliperidone extended-release tablet is a new oral antipsychotic. Its pharmacokinetic profile obviates the need for titration and is associated with improved tolerability. Furthermore, it undergoes limited hepatic metabolism. It has the potential to be a useful new option in the treatment of schizophrenia⁴. Other newer antipsychotics are in the late stages of development such as aripiprazole and bifeprunox. Preliminary studies indicate that they are similar in efficacy to currently approved drugs with potentially minor added safety benefits.

Most recently the glutamate system has been targeted with preliminary evidence suggesting efficacy of a selective metabotropic glutamate 2/3 agonist for both positive and negative symptoms.⁵

Typical antipsychotics

There are various definitions of typical and atypical antipsychotics. Here, typical antipsychotics are considered to be those drugs that tend (at antipsychotic doses) to produce EPSE. Table 1.2 shows the main typical agents, by class, and their side-effects – it should be noted that not all these agents are available in some countries.

The most potent D2 blockers, and notably those without intrinsic anticholinergic properties (e.g. haloperidol), are most likely to cause EPSE, though these effects can occur at higher doses of any of these agents. Other side-effects of the typical antipsychotics also tend to be a reflection of receptor binding. For example, those agents with potent H1 blockade tend to be sedating; those with peripheral anticholinergic (muscarinic) effects have a propensity to cause dry mouth, constipation, urinary retention, and blurring of vision; and those with alpha-adrenergic blockade can cause problematic postural hypotension. Other potential effects of these agents include weight gain, hyperprolactinemia (which can result in sexual dysfunction and galactorrhea), and lowering of the seizure threshold.

There are other particular side-effects of certain agents that might influence prescribing habits (for a comprehensive list of particular side-effects see reference 7). Of particular concern is the effect some antipsychotics have on cardiac conduction, notably prolongation of the QTc interval, with the potential for sudden death. Pimozide has long been identified in this regard, especially at high doses, and electrocardiogram monitoring is required. More recently, concern about thioridazine has led to restriction of its use in many countries and the oral form of droperidol has been withdrawn, with restrictions placed on

Table 1.2 Typical antipsychotics – relative side-effects

Drug	Adult oral max. dose (mg/day)	Relative side-effects (most will be dose related)						
		Anticholinergic	Cardiac	EPSE	Hypotension	Sedation	Minor O/D	Weight gain
		Prolactin Proconvasant						
Phenothiazines								
Chlorpromazine	1000	+++	++	++	++	++	++	++
Levomepromazine (methotrimeprazine)	1000	+++	++	+++	+++	+++	?	++
Promazine	800	++	++	+	++	++	?	++
Pericyazine	(300)	+	++	+	+++	+++	?	++
Thioridazine	600	++	+++	+	++	++	++	++
Fluphenazine	20	++	++	+++	+	++	+	+
Perphenazine	24	+	++	+++	+	++	+++	++
Trifluoperazine	—	+/-	++	+++	+	+	++	+
Butyrophenones								
Benperidol	1.5	?	?	?	++	?	?	+
Haloperidol	30	+	++	+++	+	+	+	+
Thioxanthines								
Flupenthixol	18	++	+/-	++	+/-	+	?	+
Zuclopenthixol	150	++	+	+++	+	++	?	+/-
Diphenylbutylpiperidine								
Pimozide	20	+	+++	++	++	+	+/-	+
Substituted benzamides								
Sulpiride	2400	+	+/-	+	+/-	+	+	+/-
Dibenzoxazepine								
Loxapine	250	++	+	+++	+	++	+	++

EPSE, extrapyramidal side-effects; O/D, overdose
+++, Marked effect; ++, moderate effect; +, mild/transient effect; +/-, little or nothing; ?, no information.
Adapted from reference 6.

the use of the parenteral form, in some countries. Other side-effects are less dangerous but also affect prescribing. For example, chlorpromazine results in a photosensitivity that makes its use in sunny climes problematic, while thioridazine at high doses over prolonged usage can result in retinitis pigmentosa.

Atypical antipsychotics

A number of agents have now been developed that demonstrate antipsychotic efficacy at doses that do not usually result in EPSE. These agents are often referred to as either novel or atypical antipsychotics. To avoid confusion with clozapine, which is the archetypal atypical antipsychotic, these agents are referred to here as novel atypicals; when clozapine is grouped with them, they are jointly referred to as atypicals. It should be emphasized, however, that this group contains a number of drug types, with differences in receptor-binding profiles, different side-effects, and possibly differential efficacies against particular symptoms in different patients. The main current drugs in this group, along with side-effects, are given in Table 1.3; again, not all drugs are available in all countries. It should be noted that a usual dose range is provided for each agent. This is on the basis of the literature and clinical experience, and does not preclude the use of lower or higher doses in some patients, e.g. low doses are often used in the elderly and higher doses in partial responders. As always, the judgment about dosing is based on clinical response and side-effect burden.

It is still unclear as to which drug would be most beneficial for each individual patient, and often clinical trial and error guides therapeutic interventions. Certainly, efficacy against positive psychotic symptoms seems to be similar between agents; clozapine has some advantage for negative symptoms³ (Chapter 3) and amisulpride at low dose (50–300 mg/day) also has benefit for negative symptoms⁸. In clinical practice, it is the side-effect profile that probably plays the main part in the determination of drug choice, e.g. sedation and weight gain with olanzapine, the problems of EPSE at high doses, and raised prolactin levels with risperidone, and the potential for cardiac conduction problems with ziprasidone and sertindole might mitigate against the use of each of these agents for particular patients. Particular concern has been raised by the propensity of the dibenzodiazepines in particular to be associated with weight gain, diabetes, and dyslipidemia (see Chapter 6). In patients with additional risk factors for these outcomes, aripiprazole or ziprazidone might have particular benefits. Stahl¹³ provides useful clinical pearls of wisdom about these agents.

Table 1.3 Atypical antipsychotics – relative side-effects

Drug	Adult oral max. dose (mg/day)	Relative side-effects (most will be dose related)							
		Anticholinergic	Cardiac	EPSE	Hypotension	Sedation	Minor O/D	Weight gain	Prolactin
Clozapine	900	+++	+++	+/-	+	+++	?	+++	+/-
Olanzapine	20	+	+/-	+/-	+/-	++	+/-	+++	+
Quetiapine	750	+	+	+/-	+	+	?	+	+
Risperidone	(16)	+/-	+/-	++	+	+	?	+	++
Zotepine	300	++	++	+	++	++	?	+++	+++
Sertindole	(20)	+/-	++	+/-	++	+/-	+/-	++	+/-
Amisulpride	1200	+/-	+/-	+	+/-	+/-	+/-	+	+
Aripiprazole	30	+/-	+/-	+/-	+/-	+/-	?	+	+/-
Ziprasidone	160	+	++	++	+	+	?	+	+
Paliperidone*	12	+/-	+/-	+	+	+/-	?	+/-	+

EPSE, extrapyramidal side-effects; O/D, overdose

+++, Marked effect; ++, moderate effect; +, mild/transient effect; +/-, little or nothing; ?, no information.

*based on Owen RT. Extended release paliperidone: efficacy, safety and tolerability profile of a new atypical antipsychotic. *Drugs of Today* 2007; 43:249–58.

Other data adapted from reference 6, with permission.

Treatment approaches to early episode psychosis

The atypical antipsychotics have revolutionized the pharmacological management of early episode psychosis and are promoted by most clinicians as the drugs of first choice in such patients. Fig. 1.1 shows a treatment algorithm for a patient in their first episode of illness. It should be noted that novel atypical agents are promoted first line and if one atypical fails, or produces intolerable side-effects, then a trial of at least one different novel atypical is suggested before reverting to either a typical agent or clozapine. In some countries, notably France, amisulpride is used as a first line for many patients and has a low side-effect burden although hyperprolactinemia is relatively common and EPSE can occur at higher doses (Table 1.3). Some clinicians believe that typical agents are more potent than atypicals for some patients and would use these before clozapine; others believe that the particular benefits that can accrue with clozapine treatment should sway clinicians to use this agent earlier in treatment⁹. Of course, the role of non-pharmacological treatments in the management of schizophrenia in general, and early psychosis in particular, cannot be understated (details of such approaches can be found elsewhere in this book). Chapter 15 outlines a comprehensive approach to the management of a patient with early episode psychosis.

Treatment of relapse of psychosis

For patients who are established on a typical antipsychotic and who experience a relapse of psychosis, a suggested treatment algorithm is presented in Fig. 1.2. The rationale is that if the prior agent was effective and well tolerated, then that agent should be reinstituted. Having said this, many clinicians would consider relapse as an opportunity to change to an atypical antipsychotic. Certainly, if the patient was either inadequately controlled or experienced EPSE or TD on the typical agent, a change to an atypical agent should be considered. It is also important to ascertain the cause of the relapse: if it was due to non-adherence to medication, then this would need to be investigated, and if side-effects were a contributing factor, this would sway one to change to an atypical antipsychotic. A systematic review and meta-analysis of randomized controlled trials by Leucht et al¹⁰ revealed that rates of relapse and overall treatment failure were moderately but significantly lower with atypical antipsychotics.

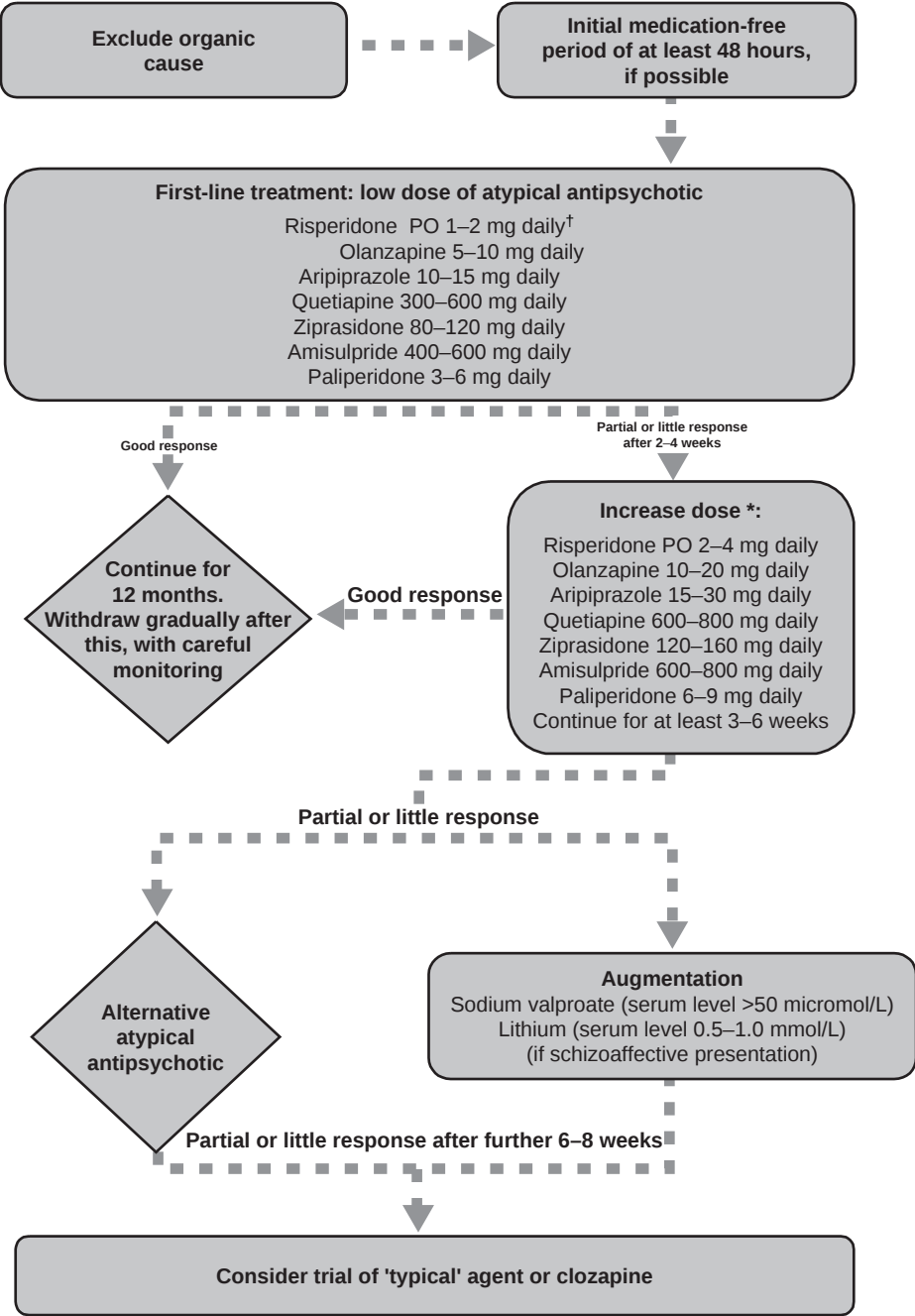


Figure 1.1 Treatment guidelines: early episode psychosis. *Dose recommended may be above licenced doses. Clinicians should check local prescribing information before use.
[†]If adherence problematic, may consider long-acting IM Risperidone 25–50mg. Oral cover is needed for the first 3–4 weeks, and tapered over weeks 4–5.

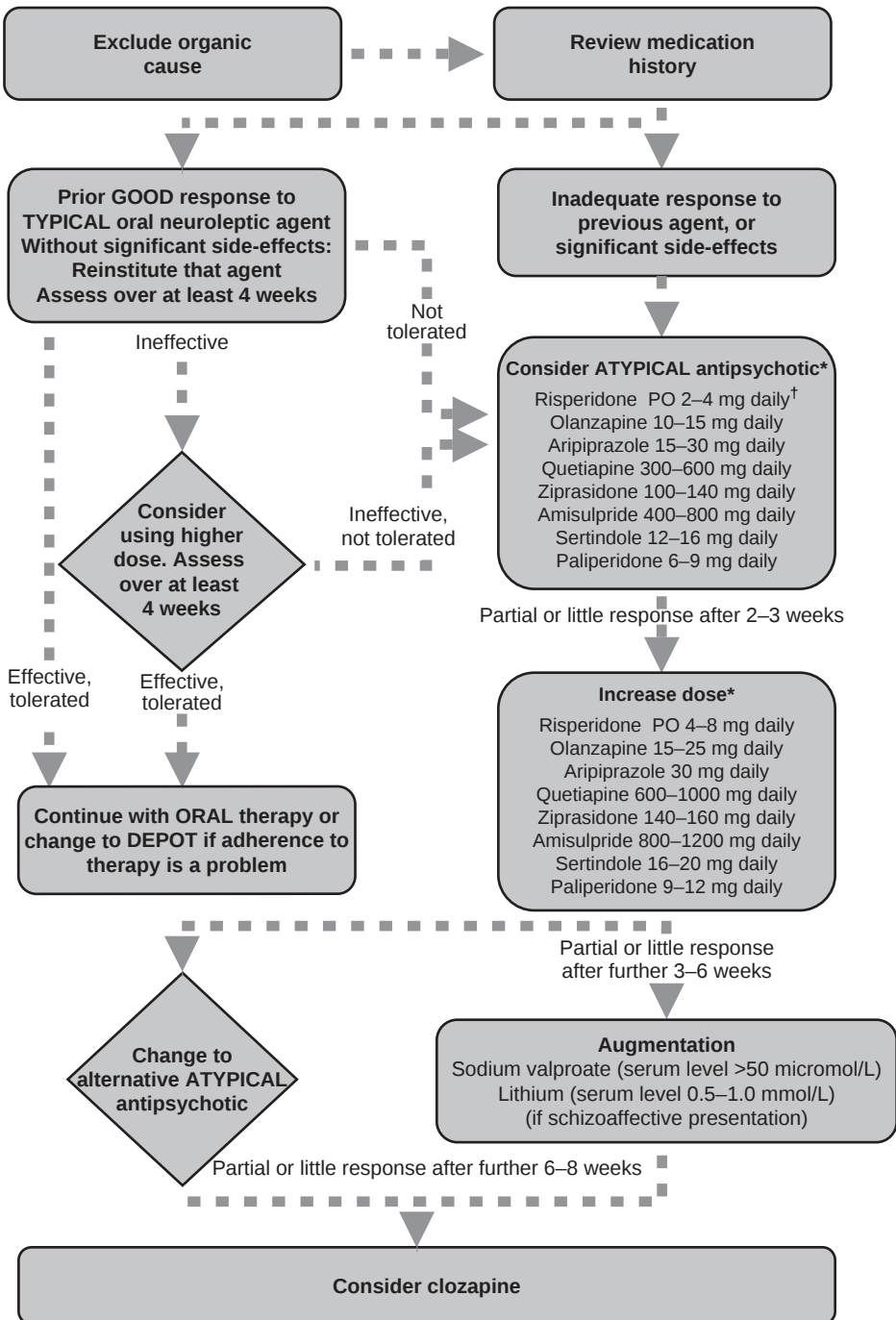


Figure 1.2 Treatment guidelines: relapse or exacerbation of schizophrenia. *Dose recommended may be above licenced doses. Clinicians should check local prescribing information before use. [†]If adherence problematic, may consider long-acting IM Risperidone 25–50mg. Oral cover is needed for the first 3–4 weeks, and tapered over weeks 4–5.

Treatment resistance and the place of clozapine

In terms of response to medication, the criteria for treatment resistance in schizophrenia usually include at least two failed treatment trials with antipsychotics from at least two different classes¹¹. The domains usually assessed are psychotic symptoms but, given the scope of symptoms and disabilities associated with schizophrenia, it is important to look at the individual in a holistic manner, including associated symptoms such as depression and anxiety, as well as relationships, social and occupational functioning, and overall quality of life. Here, attention is given to the role of medication in treatment resistance. First, the role of clozapine is considered and then pharmacological augmentation strategies. The reader is referred to other chapters in this book for broader psychological and social aspects of the treatment of persistent symptoms and disabilities in schizophrenia. Chapter 16 provides a comprehensive approach to a patient with treatment-resistant psychosis.

As discussed above, clozapine was the first atypical antipsychotic in that it does not cause EPSE at therapeutic doses and is associated with an apparent negligible rate of TD. It also appears to have particular benefit in the treatment of patients who have failed to respond to other antipsychotics, i.e. those who are considered to be treatment resistant. There is also some evidence to suggest that clozapine has particular efficacy against the negative symptoms of schizophrenia and might enhance some domains of cognitive function (see Chapters 3 and 4). Clozapine's particular place in the management of treatment-resistant patients has been underscored by the recent Clinical Antipsychotic Trials for Interventions Effectiveness (CATIE) trial¹². In that study, patients who received clozapine after discontinuation of two previous antipsychotics were less likely to discontinue treatment due to inadequate therapeutic response, than patients who received quetiapine, risperidone, or olanzapine.

Clozapine does, however, produce a number of side-effects that limit its use. Most dangerous of these is agranulocytosis, which can be fatal. This potential hazard is addressed by blood monitoring, as outlined in Fig. 1.3 (note that monitoring regulations differ between countries, but the principles remain the same). Other side-effects include sedation, weight gain, sialorrhea, and lowering of the seizure threshold, which can result in convulsions, particularly at high doses. Hypotension, tachycardia, and cardiac conduction abnormalities can also occur¹³. It should be noted that some or all of these last-mentioned effects can occur to a greater or lesser extent with many other

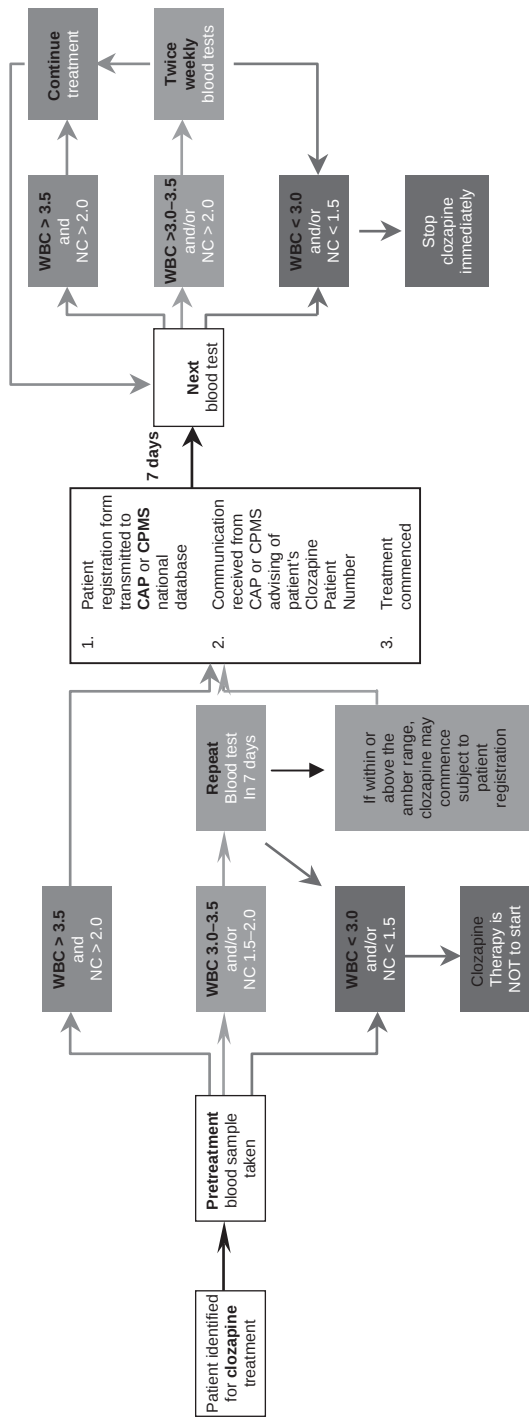


Figure 1.3 Flow chart for treatment commencement and maintenance on clozapine (Australian protocol). WBC, total white blood cell count; NC, neutrophil cell count; CAP, Clozapine Alert Program (FH Faulding); CPMS, Clozaril Patient Monitoring System (Novartis). Note: (1) all patients must be registered with either the CAP or CPMS national database; (2) All patients must have blood tests at least weekly for 18 weeks, then at least every 4 weeks thereafter; (3) extra blood tests, immediately and twice weekly, are required if symptoms of infection are observed, e.g. sore throat and mouth ulcers; (4) if treatment is stopped for non-hematological reasons, patients on weekly monitoring should continue blood-monitoring at least weekly for 4 weeks; patients on monthly monitoring should have one further blood count 4 weeks after ceasing treatment; (5) only medical officers and pharmacists registered with the CAP or CPMS databases may prescribe and dispense clozapine; (6) for further information please refer to the CAP or CPMS protocol which may vary in different countries. Check with national clozapine registration center prior to prescribing.

antipsychotics (Tables 1.2–1.4). There is also a risk, albeit low, of potentially fatal myocarditis and cardiomyopathy for which some centers have introduced regular cardiac monitoring for patients on clozapine¹⁴.

Furthermore, patients who discontinue clozapine abruptly often experience a withdrawal reaction, in part mediated by cholinergic rebound¹⁵ and in part due to rapid displacement of clozapine from dopamine receptors¹⁶. There is also clinical evidence that once patients have discontinued clozapine and relapsed, then their chance of responding to rechallenge with clozapine is reduced. Because of these factors, patients on clozapine should be accepting of treatment and close cooperation with the treating team is important. A suggested process for engagement and monitoring of patients on clozapine has recently been published¹³. In cases where there is an inadequate response to clozapine, a number of augmentation strategies might be considered (see below).

Augmentation strategies

Another approach to treatment resistance is augmentation with another psychotropic agent. Whilst often applied in clinical practice, there is still a very limited research database on such strategies, and these interventions are usually guided by clinical intuition and experience. One issue that is particularly controversial is the use of typical and atypical agents together. This is perhaps most common in people who are on a typical depot medication and an oral atypical. Whilst an anathema to pharmacological purists, and not to be promoted in most cases, some patients do seem to benefit from such combinations and withdrawal of either agent can result in relapse. Many clinicians use other combinations of antipsychotics. In treatment-resistant patients, the combination of clozapine and a relatively specific, 'tight' D2 binding atypical antipsychotic, such as risperidone, sulpiride, or amisulpride¹⁷ has gained some popularity, though there is the potential risk of a greater side-effect burden¹⁸, and the research evidence is rather equivocal. For example, a recent double-blind, placebo-controlled study by Josiassen et al¹⁹ compared clozapine/placebo with clozapine/risperidone (6 mg) over 12 weeks in patients who had been partially responsive to clozapine, and showed a significantly greater improvement for the risperidone arm in terms of the number of positive and negative symptoms. However, a separate randomized, placebo-controlled, double-blind trial of augmentation of clozapine (>400 mg for at least 12 weeks) with risperidone 3 mg showed a 26% rate of response

(i.e. greater than 20% decline in total positive and negative syndrome score (PANSS)) in the placebo arm compared with 18% response in the risperidone group²⁰. Quetiapine has also been used as an adjunct to clozapine, with the added benefit of being able to reduce clozapine dose and potentially alleviate weight gain and improve glycemic control in patients who develop diabetes²¹. Aripiprazole augmentation has also been trialled²², and in clinical practice may have a place in patients on clozapine who develop the metabolic syndrome.

Another fairly common strategy is to augment with a mood stabilizer, usually lithium²³, carbamazepine²⁴ or sodium valproate²⁵, especially in individuals who show an affective component to their illness. Such combinations are usually well tolerated and can arguably 'spare' antipsychotics in that the dose required might be lower than if the antipsychotic is used alone. Lithium can increase the neurotoxicity of antipsychotics, notably clozapine, and thus its use in combination requires caution²⁶. Carbamazepine can be problematic as it induces the metabolism of a number of hepatic enzymes, thus affecting levels of other drugs; it is also contraindicated with clozapine, due to the propensity to bone marrow suppression.

Evidence that the addition of antidepressants to antipsychotics is useful for enduring negative symptoms is equivocal¹⁸. Selective serotonin reuptake inhibitors (SSRIs) such as fluvoxamine or fluoxetine when combined with typical antipsychotics have shown some improvement in negative symptoms, but again not all studies concur. A study comparing mirtazapine with placebo in addition to haloperidol in patients with stable schizophrenia but prominent negative symptoms showed a significant reduction (43%) in negative symptoms in the mirtazapine group with no significant effect on depressive symptoms²⁷; this study requires replication. Care needs to be taken with some combinations, e.g. with fluvoxamine and clozapine as the former causes elevations in the serum levels of the latter due to CYP1A2 inhibition. Also, some tricyclics have been associated with an exacerbation of psychotic symptoms in some individuals. Other augmentation strategies have also been investigated, with mixed results: those targeting negative symptoms are outlined in Chapter 3 and those aiming to enhance cognition in Chapter 4. Table 1.5 summarizes pharmacological augmentation strategies in schizophrenia.

Electroconvulsive therapy has also been used in treatment-resistant cases, in combination with antipsychotics, and there is some evidence of additional benefit in terms of antipsychotic effect as well as prevention of relapse^{28,29}. The use of high doses of antipsychotics (above British National Formulary

Table 1.4 Depot antipsychotics – relative side-effects

Drug	Adult oral max. dose (mg/day)	Relative side-effects (most will be dose related)								
		Anticholinergic	Cardiac	EPSE	Hypotension	Sedation	Minor O/D	Weight gain	Prolactin	Proconvulsant
Typical										
Fluphenazine decanoate	100 (2/52)	++	++	+++	+	++	+	+	++	+
Pipotiazine palmitate	200 (4/52)	++	++	++	+	+	?	?	++	++
Haloperidol decanoate	300 (4/52)	+	++	+++	+	+	+	+	++	+
Flupenthixol decanoate	400 (1/52)	++	+/-	++	+/-	+	+	?	++	+
Zuclopenthixol decanoate	600 (1/52)	++	+	+++	+	++	++	?	++	+/-
Fluspirilene	20 (1/52)	+	+	++	++	++	?	?	++	+
Atypical										
Risperidone	50 (2/52)	+/-	+/-	+	+	+	?	+	++	+/-

EPSE, extrapyramidal side-effects; O/D, overdose
+++, Marked effect; ++, moderate effect; +, mild/transient effect; +/-, little or nothing; ?, no information.
Adapted from reference 6.

Table 1.5 Summary of evidence for different augmentation strategies

Augmentation strategy	Evidence/results
Relatively selective D2 blockers e.g. risperidone, amisulpride added to clozapine	? Decrease in positive and negative symptoms: mixed findings (see text)
Lithium	Three early studies – benefit Five later studies – no benefit
Sodium valproate	Inconsistent results – particular efficacy for aggression and affective symptoms
Carbamazepine	No clear benefit
Antidepressants	Fluvoxamine/fluoxetine + typical agent – decrease in negative symptoms Fluoxetine + clozapine – no clear benefit for negative symptoms Sertraline/citalopram + typical agent – no clear benefit for negative symptoms Mirtazepine + typical agent – decrease in negative symptoms (single study)
Benzodiazepines	Inconsistent results – no clear benefit
Nicotine (patches)	Cognitive benefits (attention and concentration)
Stimulants	? Benefit for negative/cognitive symptoms but carry potential risk of increasing positive symptoms
Apolipoprotein E	Inconsistent results
Glutamatergic agents	? Decrease in negative symptoms: requires further study

Adapted from reference 11.

(BNF) guidelines; see Tables 1.2–1.4) is not usually recommended due to the risk of potentially dangerous side-effects³⁰.

Switching antipsychotics

In patients with an established illness and who are well controlled on a typical agent, there is much controversy about whether they should be changed over to atypicals. Any change carries with it the possibility of relapse,

and patients and their families should be fully informed of this before any such changeover is instituted. Close monitoring of mental state is also required during this phase. Ultimately, the decision about switching depends upon:

- efficacy of current medication, in treating both positive and negative symptoms;
- side-effects being experienced (emergent TD is particularly worrisome in patients on typical agents);
- clinical judgment;
- patient preference.

In general, a slow crossover over 2–6 weeks is best tolerated, especially if:

- switching from a high dose to a high dose agent;
- changing from a 'loose' D2 binding agent, such as clozapine or quetiapine;
- side-effect profiles of the two agents are markedly different.

Tables 1.2–1.4 summarize side-effect profiles of antipsychotic agents. Box 1.1 outlines specific problems that might be encountered in switching, and suggested strategies to deal with these.

In patients on depots, the usual strategy is to commence the new agent in place of the depot at the time the next depot was due.

The place of depot antipsychotics

Due to problems of adherence amongst patients with schizophrenia and related disorders (see Chapter 10), depot formulations are widely used. These are formulations in an oily base (typical antipsychotics) or an aqueous solution containing the active agent in a matrix of glycolic acid (risperidone), which should be injected deep into the gluteal muscle. These formulations are effective for 1–4 weeks, depending on the constitution and the individual. The main depot formulations are detailed in Table 1.5. Although a meta-analysis by Adams et al³¹ concluded that there is little to choose between the different typical depot formulations in terms of efficacy and side-effects, some patients do seem to benefit and/or tolerate particular agents better than others, and failure of response and/or intolerable side-effects of one depot should not preclude the trial of another.

Box 1.1 Problems that may occur with switching.

The new agent is not effective or insufficient tolerability: since antipsychotic efficacy may take some time do not abandon the new agent too quickly. In addition, side-effects tend to be worse initially; hence, try to deal with them in the short term rather than abandon the new agent too soon. Showing patients the schematic below can assist in the educational process in this regard

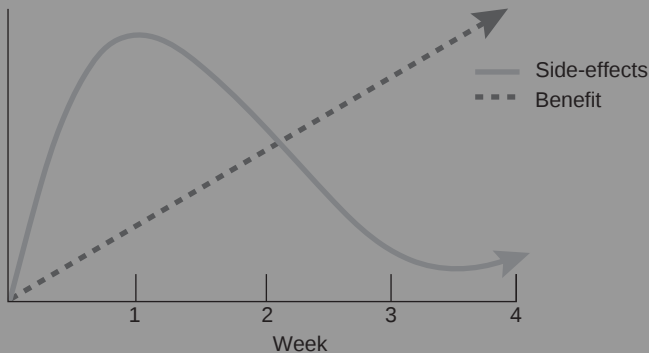


Figure 1.4 Schematic representing time course of side-effects vs. clinical benefit.

Cholinergic rebound: flu-like symptoms with malaise, agitation, anxiety, insomnia, gastrointestinal upset can occur if switching from agent with high M1 binding (e.g. clozapine) to one with a low M1 binding (e.g. risperidone, amisulpride, aripiprazole). Slow crossover is required and use of short-term anticholinergic such as benztropine or benzhexol is recommended

'Rebound': psychosis or extrapyramidal side-effects: more likely to occur if switching from 'loosely bound' agent such as clozapine or quetiapine and normally occurs quicker than one would expect from true psychotic relapse. Cross-titrate slowly and symptomatic treatment with a beta-blocker or benzodiazepine if warranted

'Rebound' insomnia: more likely if changing from more sedating agents (olanzapine, clozapine) to less sedating agents (risperidone, amisulpride, aripiprazole). Administration of the new medication in the morning rather than the evening and short-term hypnotic such as zolpidem or zopiclone is acceptable

The problems with depot use include the potential disempowerment of the patient (though some patients prefer depots to oral medication), pain at the injection site, and difficulties if side-effects are experienced (because they are long acting). Having said this, depot formulations undoubtedly have a place in treatment and can be a crucial factor in treatment adherence³¹.

Recently, the first long-acting atypical antipsychotic, long-acting risperidone injection, has become available. Several short- and long-term studies have provided evidence of its safety and efficacy. A 12-week placebo-controlled trial of acute patients by Kane et al³² showed good symptom improvement and a low incidence of side-effects. In addition, a separate 1-year double-blind study of two doses (25 mg and 50 mg) of long-acting risperidone injection by Simpson et al³³ also showed low relapse and rehospitalization rates. Currently, a depot form of olanzapine is also in development. It is probable that depot atypicals will come to play a key role in the maintenance treatment of schizophrenia, notably in those patients with a history of poor adherence to oral agents.

What is also not often appreciated is that some of the typical depots take up to 3 months to reach a steady state³⁴. Various strategies might be employed to address this problem, including a reduced dose interval (e.g. weekly for 4 weeks, then fortnightly) or supplementation with an oral agent during this phase. Long-acting injectable risperidone, on the other hand, has no significant drug release for the first 3–4 weeks, with a peak at 4–6 weeks; with repeated injection every 2 weeks, steady state levels are usually reached by weeks 6–8³⁵. Thus, oral cover is needed for the first 3–4 weeks, and tapered over weeks 4–5.

Complications of antipsychotic treatment and how to deal with them

The main side-effects of the antipsychotic agents in current use are shown in Tables 1.2–1.4. These side-effects can be very debilitating for the patient and can lead to non-adherence. Thus, patients should be warned about the possibility of side-effects, and every effort should be made to recognize and treat side-effects as soon as they appear.

A particularly dangerous, though rare, side-effect is neuroleptic malignant syndrome (NMS), usually associated with high doses of typical antipsychotics in an aroused patient, though it has also been reported with low doses and with atypical agents³⁶. The syndrome is characterized by muscle rigidity, pyrexia, autonomic instability, and alteration in consciousness; blood tests show an elevated white cell count and a raised creatine phosphokinase (CPK) level. Immediate withdrawal of the antipsychotic agent and treatment, either supportively or with bromocriptine and/or dantrolene, is required³⁶.

Box 1.2 details some strategies that might be used to counter some of the more common complications of treatment with antipsychotic drugs.

Box 1.2 Guidelines for dealing with complications of treatment of patients with schizophrenia.

Agitation

Add short-term oral benzodiazepine, e.g. clonazepam 1–2 mg, diazepam 5–10 mg, or lorazepam 1–2.5 mg

Arousal/acute behavioral disturbance

Specific strategies as outlined in Chapter 8

Insomnia

Add short-term oral benzodiazepine, e.g. temazepam 10–20 mg, clonazepam 1–2 mg, diazepam 5–10 mg, or hypnotic, e.g. zopiclone 7.5 mg, zolpidem 5–10 mg, or zolpidem controlled release 6.25–12.5 mg

Acute dystonic reaction

Add anticholinergic agent, e.g. benztropine 2 mg intramuscularly or intravenously, up to a maximum of 6 mg in 24 hours

Chronic parkinsonism

Add regular oral anticholinergic agent, e.g. benztropine 1–2 mg/day, benhexol 2 mg tds, biperiden 1–2 mg tds

Akathisia

Reduce dose of antipsychotic if possible. If still present add propranolol 10 mg bd, anticholinergic, clonidine 50–100 upright µg bd, or a benzodiazepine

Neuroleptic malignant syndrome

After this syndrome has occurred and been treated consider atypical antipsychotic; monitor closely

Tardive dyskinesia

Consider changing to atypical antipsychotic or clozapine

Persistent negative symptoms (see Chapter 3)

Determine whether due to primary (deficit) symptoms, or to secondary negative symptoms (e.g. response to positive symptoms, medication induced, or due to depression)

If secondary ensure optimal treatment of positive symptoms and/or underlying depression, consider changing to atypical antipsychotic

If primary consider change to atypical antipsychotic

Intervening persistent depression

Add antidepressant, e.g. selective serotonin reuptake inhibitor (SSRI)

Continual non-compliance

Establish reasons for non-compliance. Educate patient and family about rationale for ongoing treatment. Educate patient about side-effects of antipsychotic medication and treat these vigorously. Treat any underlying depression. Consider role for atypical antipsychotic.

If justified, consider depot antipsychotic

Illicit substance use

Counseling and specific measures (see Chapter 6). Clozapine might have a particular role

Conclusions

These are exciting times for the pharmacological management of schizophrenia and related disorders, with the atypical antipsychotics allowing good symptom control with a far lower propensity to motor side-effects than many of the older agents. However, pharmacological treatment remains only one part of what should be a comprehensive biopsychosocial approach to the management of people with this group of conditions. Other chapters in this book address these components of treatment.

References

1. Lieberman JA, Stroup TS, McEvoy JP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; 353: 1209–23.
2. Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatment of schizophrenia: a critical review of pharmacology and mode of action of antipsychotic. *Mol Psychiatry* 2005; 10: 79–104.
3. Stahl SM. Selecting an atypical antipsychotic by combining clinical experience with guidelines from clinical trials. *J Clin Psychiatry* 1999; 60 (Suppl 10): 31–41.
4. Kane J, Canas F, Kramer M et al. Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. *Schizophr Res* 2006; 90: 147–61.
5. Patil ST, Zhang L, Martenyi F, et al. Activation of mGlu 2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. *Nature Medicine* 2007; 13: 1102–7.
6. Bazire S. Psychotropic Drug Directory 2005. Salisbury, UK: Fivepin Ltd, 2005.
7. Bezchlibnyk-Butler KZ, Jeffries JJ, eds. *Clinical Handbook of Psychotropic Drugs*, 16th edn. Seattle, WA: Hogrefe & Huber Publishers, 2006.
8. Leucht S, Pitschel-Walz G, Engel RR, Kissling W. Amisulpride, an unusual ‘atypical’ antipsychotic: a meta-analysis of randomized controlled trials. *Am J Psychiatry* 2002; 159: 180–90.
9. Remington G. Rational pharmacotherapy in early psychosis. *Br J Psychiatry* 2005; 187 (Suppl 48): 77–84.
10. Leucht S, Barnes T, Kissling W et al. Relapse prevention in schizophrenia with new generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. *Am J Psychiatry* 2003; 160: 1209–22.
11. Jones S, Castle DJ. Management of treatment resistant schizophrenia. *S Afr Psychiatry Rev* 2006; 9: 17–23.
12. McEvoy JP, Lieberman JA, Stroup ST et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 2006; 163: 600–10.
13. Castle DJ, Lambert T, Melbourne S et al. A clinical monitoring system for clozapine. *Australas Psychiatry* 2006; 14: 156–68.
14. Berk M, Fitzsimmons J, Lambert T, et al. Monitoring the safe use of clozapine: a consensus view from Victoria, Australia. *CNS Drugs* 2007; 21: 117–27.
15. Wagstaff AJ, Bryson HM. Clozapine: a review of its pharmacological properties and therapeutic use in patients with schizophrenia who are unresponsive to or intolerant of classical antipsychotics. *CNS Drugs* 1995; 4: 37–40.

16. Seeman P, Tallerico T. Rapid release of antipsychotic drugs from dopamine D2 receptors: an explanation for low receptor occupancy and early clinical relapse upon withdrawal of clozapine or quetiapine. *Am J Psychiatry* 1999; 156: 876–84.
17. Agelink MW, Kavuk I, Ak I. Clozapine with amisulpride for refractory schizophrenia. *Am J Psychiatry* 2004; 161: 924–5.
18. Goff DC, Freudenreich O, Evins E. Augmentation strategies in the treatment of schizophrenia. *CNS Spectr* 2001; 6: 904–11.
19. Josiassen RC, Joseph A, Kohegyi E et al. Clozapine augmented with risperidone in the treatment of schizophrenia: a randomised, double-blind, placebo-controlled trial. *Am J Psychiatry* 2005; 162: 130–6.
20. Honer W, MacEwan GW, Chen EY et al. A randomized, placebo-controlled, double-blind trial of augmentation of clozapine with risperidone. *International Congress on Schizophrenia Research [abstract]*. *Schizophr Bull* 2005; 31(2): 487.
21. Reinstein MJ, Sirotovaskaya LA, Jones LE et al. Effect of clozapine-quetiapine combination therapy on weight and glycaemic control. *Clin Drug Invest* 2003; 18: 99–104.
22. Ziegenbein M, Wittmann G, Kropp S. Aripiprazole augmentation of clozapine in treatment-resistant schizophrenia. *Clin Drug Invest* 2006; 26: 117–24.
23. Small JG, Klapper MH, Malloy FW et al. Tolerability and efficacy of clozapine combined with lithium in schizophrenia and schizoaffective disorder. *J Clin Psychopharmacol* 2003; 23: 223–8.
24. Leucht S, McGrath J, White P, Kissling W. Carbamazepine augmentation for schizophrenia: how good is the evidence? *J Clin Psychiatry* 2002; 63(3): 218–24.
25. Basan A, Leucht S. Valproate for schizophrenia. *Cochrane Database Syst Rev* 2004; (1): CD004028.
26. Psychotropic Writing Group. *Therapeutic Guidelines: Psychotropic, Version 5*. Therapeutic Guidelines Ltd: Melbourne; Australia, 2003.
27. Berk M, Ichim C, Brook S. Efficacy of mirtazapine add on therapy to haloperidol in the treatment of the negative symptoms of schizophrenia: a double-blind randomized placebo-controlled study. *Int Clin Psychopharmacol* 2001; 16: 87–92.
28. Rasmussen KG. When is ECT indicated in psychiatric disorders? *Curr Psychiatry* 2002; 1: 21–6.
29. Keuneman R, Weerasundera R, Castle D. The role of ECT in schizophrenia. *Australas Psychiatry* 2002; 10: 385–8.
30. Morrison DP. Management of treatment refractory schizophrenia. *Br J Psychiatry* 1996; 169 (Suppl 31): 15–20.
31. Adams CE, Fenton MKP, Quraishi S, David AS. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *Br J Psychiatry* 2001; 179: 290–9.
32. Kane JM, Eerdeken M, Lindenmayer J-P et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry* 2003; 160: 1125–32.
33. Simpson GM, Mahmoud RA, Lasser RA et al. A 1-year double-blind study of 2 doses of long-acting risperidone in stable patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry* 2006; 67: 1194–203.
34. Ereshefsky L, Saklad SR, Tran-Johnson T et al. Kinetics and clinical evaluation of haloperidol decanoate loading dose regimen. *Psychopharmacol Bull* 1990; 26: 108–14.
35. Knox ED, Stimmel GL. Clinical review of a long-acting, injectable formulation of Risperidone. *Clin Ther* 2004; 26: 1994–2002.
36. Farver DK. Neuroleptic malignant syndrome induced by atypical antipsychotics. *Expert Opin Drug Saf.* 2003; 2: 21–35.

Psychological approaches to the management of persistent delusions and hallucinations

Til Wykes, Gina Smith, and Craig Steel

As more effective treatments for schizophrenia have evolved, emphasis has started to be placed on defining treatments for the individual symptoms rather than on the whole schizophrenia syndrome. The hallmark positive symptoms, i.e. hallucinations and delusions, are a case in point. Although the severity of these symptoms may be controlled by medication, it is not uncommon for them to persist, or at least to reappear in subsequent relapses, despite adequate doses of medication. For some patients the effects of medication on positive symptoms include making them less anxious about the symptoms (this is particularly so for delusions), and allowing them to ‘ignore’ the symptoms so they can concentrate on their domestic and social lives. Others describe their ‘voices’ as getting quieter and less frequent with medication. But for about one-third of patients, the positive symptoms continue despite adequate levels of antipsychotic drugs. These symptoms are distressing, and can have dramatic effects on the person’s quality of life and their dependence on psychiatric care.

Symptomatic control by medication also has its costs, particularly at high doses (i.e. side-effects), as well as benefits (see Chapter 1). Thus, alternative forms of therapy have been investigated as adjuncts to antipsychotic medication for the control of hallucinations and delusions. Patients and relatives have welcomed these therapies and have put pressure on psychiatric services to provide them as part of a comprehensive service.

The evolution of psychological therapies has been driven by the development of psychological models of the individual symptoms of schizophrenia. Such models have enabled psychologists to establish theories of the mechanisms of the development and maintenance of these symptoms. Together with consideration of the characteristics of these symptoms, such as the levels of conviction for delusions and the physical attributes of the voices, this has led to specific treatment approaches¹⁻³.

Psychological approaches to the reduction of hallucinations

Even though various types of hallucination are experienced by people with schizophrenia, auditory hallucinations are the most prevalent with 75% of people with a diagnosis of schizophrenia experiencing them at some stage of their illness⁴. The majority of treatment approaches for hallucinations have therefore been aimed at the reduction of this most prevalent category of abnormal experience. Both cognitive and behavioral approaches have been applied, and more recently there have been attempts to meld the two techniques together. (Current techniques are summarized in Table 2.1.)

Early interventions were more behavioral in their approach and concentrated on providing competing stimuli which would then divert attention away from the experience of hallucinations, even including punishment techniques. Even though these interventions can reduce the experience of voices, the effect is usually only a temporary one. In fact, the simple task of keeping a diary of the experiences of hallucinations will, for some people, provide some temporary reduction in the frequency of the hallucinations.

Many psychological approaches to the amelioration of voices also aim to reduce the anxiety associated with them. Slade^{5,6} showed that not only did the voices themselves produce anxiety but also that anxiety was then often a trigger for the experience of hallucinations. He found that social anxiety in particular was associated with increases in the frequency of hallucinations and that controlling the anxiety in these social situations was associated with a reduction in the experience of voices. He then carried out a series of case studies showing that anxiety management techniques were successful in reducing anxiety and subsequently the experience of hallucinations.

Later interventions developed because of an increased interest in cognition and brain sciences which produced theories about the relationship between

Table 2.1 Psychological interventions for voices

<i>Type of intervention</i>	<i>Therapy</i>	<i>Description</i>
Competing information	Thought stopping	The person has an elastic band around their wrist and is told to snap the elastic band whenever they hear a hallucination or the person shouts 'stop it' either overtly or covertly on occurrence of the voice
	Competing auditory stimuli	Wearing a personal stereo, humming, singing and speaking out loud. Using the muscles involved in vocalization seems to be the most effective.
	Self monitoring	Keeping a diary where information is recorded concurrently with the experience. The information includes the thoughts and feeling associated with the experience of the voices
Anxiety reduction	Anxiety management	Carrying out a functional analysis of times of high anxiety then using breathing techniques and relaxation exercises to reduce these experiences Also use of systematic desensitization to reduce the impact of specific cues for anxiety
Cognitive	Belief modification	Investigating the events which activate the voice and the consequences. Exploring the content of the voice and providing alternative hypotheses to test with exploration of the evidence for the belief
	Focusing	Asking the person to concentrate on the physical attributes of the voices and then gradually encourage identification of the contents of the voice as internally generated
	Coping skills enhancement	Using a case formulation, the person is asked about the antecedents, behaviours and consequences as well as their own coping strategies for dealing with voices

brain functioning and the experience of voices (see Box 2.1). For instance, one theory suggested that hallucinations were the result of poor transfer of information across the corpus callosum, that resulted in a mismatch between the auditory experience in each ear. It was thought that an ear plug in the left ear would even up this information transfer and, in fact, those patients who wore an ear plug did report significant reductions in voices. However, it was also noticed that some people returned to the clinic with two ear plugs, having invested in a further one themselves. Others returned with the ear plug in the right ear and also reported reductions in severity of the hallucinations. It is not clear what was responsible for these reductions but on stopping the use of the earplugs the voices returned to their usual level⁷.

Although there is no generally accepted psychological model of auditory hallucinations there is an assumption that there is an underlying dysfunction in inner speech. In particular there is thought to be a problem in the ability to monitor the source (e.g. real or imagined, internal or external) of their inner speech, which leaves people vulnerable to making errors. In a recent review, Jones and Fernyhough⁸ suggest that those who experience auditory hallucinations have particular problems in tasks which demand high levels of source monitoring, such as imagining people speaking or imagining sounds. Fernyhough⁹ proposed that the deficit in source monitoring becomes relevant when low level non-verbal thought is transformed into verbal thought. When the dialog within the verbal thought is not attributed to oneself, they are experienced as the voices of other people.

As discussed above, anxiety provoking situations appear to increase the frequency of voices. In addition, the patient's level of self-esteem is thought to affect the negative content of the voice. However, there is also a third factor which affects the experience of voices – beliefs about the origin and potency of the voices. Birchwood and Chadwick¹⁰ have shown that the interpretation of the voices – in particular the perceived powerfulness of the voice – affects the severity of the distress experienced. It also seems to be related to

Box 2.1 Factors affecting the experience of voices

- underlying dysfunction in perception of inner speech ⁴⁴
- arousal (induced by social situations or particular stressors)
- beliefs about the voices

behavior associated with command hallucinations. Changing the beliefs about the powerfulness of the voice has therefore become a further focus for interventions. The therapy of changing beliefs about voices has developed into a more comprehensive treatment intervention called cognitive behavior therapy (CBT) for hallucinations; this is discussed in more detail below.

Another important development within the psychological management of voices is based on the concept of 'normalization'. Romme and Escher¹¹ publicized the fact that there were a large number of people who heard voices who had never been part of the psychiatric system. Some of these people had learnt to cope with their voices, while others found them to be a positive part of their life. Increased awareness of this previously ignored group has led to research which has focused on how the coping strategies of the non-psychiatric group compare with those of people who have been diagnosed with schizophrenia. The non-psychiatric group tend to describe a 'relationship' with their voices, in which they are more able to choose when they occur, and more in control as to how they respond. The fact that many non-patients experience hearing voices enables a process of normalization and a reduction of stigma for those who do have a diagnosis. This process is now incorporated into most modern psychological approaches, and is a fundamental aspect of group work with voice-hearers¹². A voice-hearer's movement, called the Hearing Voices Network, has grown in the UK, and publishes a variety of useful resources (www.hearing-voices.org).

Psychological interventions for delusions

For a long time it was thought that talking to patients about abnormal beliefs (delusions) was not only unhelpful but could be potentially damaging. Hence, many early therapeutic techniques for delusions entailed trying to distract the person and/or deny them attention whenever they talked about delusional beliefs. These techniques did have an effect on reducing delusional speech, but it has never been clear that there was any accompanying reduction of the ideas themselves rather than patients merely learning to talk about other things, or simply reduce their amount of speech¹³.

Some early attempts to try to change patients' beliefs, by discussing them and trying to generate alternative hypotheses about the delusions in collaboration with the patient, proved more successful than challenging the beliefs directly¹⁴. This finding led to the development of methods for changing beliefs themselves. As with the psychological interventions for hallucinations, these innovations have been fuelled by an enhanced understanding of

the dimensions of delusions, i.e. conviction, preoccupation, interference with everyday life, and distress.

Recently, other factors, e.g. underlying problems with the recognition of the mental states of others ('theory of mind'), abnormal reasoning biases (particularly jumping to conclusions on little evidence¹⁵), and the effects of poor self-esteem have led to more sophisticated therapies. The three current main intervention techniques are:

- *Belief modification:* where beliefs are ordered into levels of conviction, with the least well-held belief being tackled first, by trying to disentangle the types of evidence used to support the belief and generating alternative explanations.
- *Behavioral experiments:* these test the veracity of the delusional belief and the supporting evidence.
- *Reattribution:* this is a more recent therapy, particularly for paranoid ideation, where patients are encouraged to attribute negative events not to people but to situations, with an emphasis on the personal benefits (reduced distress) that these new explanations will bring.

It must be emphasized that the goal of all these techniques is to reduce the negative effects of abnormal beliefs on the lives of people with schizophrenia. Thus, changes in any of the dimensions of the belief will be considered a good outcome. The reason for this is that many people who have not been diagnosed with schizophrenia hold abnormal beliefs, i.e. those not considered normal outside the beliefs of a particular culture, but are not distressed by them and have a good quality of life¹⁶.

Within the past few years, research has focused on understanding paranoid delusions in particular^{17,18}. This attention is based on the fact that most distressing delusions are associated with paranoid beliefs. Freeman et al¹⁸ argue that paranoia can be understood as a 'threat belief' and as such inherently contains many of the psychological processes that are associated with a state of anxiety. Therefore a psychological approach to paranoia will need to tackle behaviors such as avoidance and safety seeking.

Cognitive behavior therapy

The main developmental roots for CBT have been in understanding and treating depression and anxiety. Two early case studies reported the application of

such techniques to schizophrenia^{19,20}, but CBT has only relatively recently been applied more rigorously, through manualized therapies, directly to psychotic symptoms. This development required changes in the presentation of the intervention, although the underlying model of change may be similar to that adopted for mood and anxiety symptoms. The main aims of CBT are to ameliorate distress, disability, and emotional disturbance as well as to reduce the chance of relapse of the acute symptoms²¹. CBT encompasses active and structured therapeutic methods and should be distinguished from psychoeducation, which tends to be simple, didactic, and educational. Simple psychoeducation packages have been shown to be ineffective for patients with schizophrenia²² and for their families²³.

Although there are specific components of CBT that would be accepted by all its proponents, these ingredients may be given in different proportions by different groups of professionals and for different patients. Those elements accepted by most therapists include:

- engagement with the patient;
- problem identification;
- agreeing on a collaborative formulation of the problems to be assessed;
- use of alternative explanations to challenge delusional and dysfunctional thoughts;
- establishing the link between thoughts and emotions;
- encouraging the patient to examine alternative views of events;
- encouraging the patient to examine the link between thoughts and behavior;
- use of behavioral experiments to reality test;
- setting of behavioral goals and targets;
- developing coping strategies to reduce psychotic symptoms;
- development and acquisition of relapse prevention strategies.

Further elements incorporated by some therapists include:

- improvement in self-esteem;
- increasing social support and social networks;
- schema-focused therapy.

A number of cognitive models of schizophrenia have recently been developed^{24,25} which have attempted to integrate our current understanding of a

number of psychological processes. These models establish the basis of a formulation based approach which has led to a number of clinical casebooks^{26,27}.

What are the outcomes from cognitive behavior therapy?

There have now been more than 30 randomized control trials which evaluate the effect of CBT on the positive symptoms of schizophrenia, with the majority of participants being chronic and having medication-resistant symptoms. Many of these studies, however, have had methodological problems such as non-blind rating of symptoms which is known to inflate the effectiveness. The studies also adopt different methods for evaluating the efficacy of the therapy, choosing different rating scales and sometimes idiosyncratic methods which would be difficult to replicate (for a review of methodological problems in 22 randomized controlled trials see reference 28). Despite these reservations the various meta-analyses all suggest that CBT does have an effect on symptom levels which is durable after treatment has been discontinued²⁸⁻³⁰. Average effect sizes (the amount of change expected following treatment) found in the meta-analyses ranged from 0.3 to 0.57.

One of most methodologically rigorous randomized controlled trials reviewed, a study of first- and second-episode patients carried out at the University of Manchester (SoCRATES), evaluated the effect of CBT for patients in the acute phase of their illness. There were small but measurable effects in the first few weeks of admission in the reduction of acute symptoms, particularly hallucinations. However, these short-term effects disappeared as the control conditions caught up with the CBT group. Over an 18-month period following cessation of treatment, improvements in symptom scores were evident, but overall relapse rates were not diminished³². Valmaggia et al³² found improvements in psychotic symptoms post-treatment, although these were not maintained at follow-up. It should be stressed that the fact improvements are not maintained after cessation of treatment is not grounds to conclude that the treatment does not work. Tarrier et al^{33,34}, Kuipers^{35,36}, and Sensky³⁷ all demonstrated overall symptom improvements from CBT, with hallucinations proving to be more difficult to change than delusions.

Most published studies suggest improvements in positive symptoms for CBT interventions which last at least 20 sessions and are provided by highly trained and supervised therapists. However, more recently there have been studies investigating whether mental health professionals can be trained to deliver briefer CBT interventions, thus making the therapy available to more patients. While there is evidence that training mental health nurses to deliver

brief CBT leads to a durable improvement in negative symptoms, insight, depression, and readmissions, psychotic symptoms showed no improvement^{39,40}. Similarly a randomized controlled trial investigating group CBT for voices found that only therapy provided by highly experienced therapists who received expert supervision reduced auditory hallucinations, although an improvement in social functioning was found from therapy delivered by both highly experienced and less experienced therapists¹².

Another strategy that has been investigated to try to increase the number of people with access to treatment is to deliver CBT in a group format. As mentioned above, Wykes et al¹² found an improvement in voices when group CBT was delivered by highly experienced therapists. In a randomized controlled trial between group CBT and treatment as usual in which more global positive symptoms were targeted no significant difference was found, although group CBT did reduce feelings of hopelessness and low self esteem⁴¹.

Whilst the evidence for the effectiveness of CBT for psychosis is generally positive, there are some areas which remain unclear. This is partly due to research trials incorporating different types of intervention aimed at different stages of the disorder. Also, evidence appears to be strongest when the group to receive treatment is more specifically defined, such as Trower et al's study⁴¹ which focused specifically on those individuals who heard command hallucinations.

Despite the lack of support for cheaper alternatives to individual CBT interventions delivered by highly trained therapists, CBT has been shown to be an economical treatment for psychotic symptoms of schizophrenia. Studies that have evaluated the cost-effectiveness or cost-utility of psychological interventions for the symptoms of schizophrenia have shown that providing CBT as an adjunct to standard care is not expensive, and may even be cost-effective^{37,43}.

A note about psychological treatments

The success of medication treatments for chronic disorders such as schizophrenia is based on an acute treatment and prevention model, in the same way that diabetes and asthma treatments are evaluated. So, it would be expected that withdrawal of a drug that reduces symptoms would be followed by the return of the symptoms. However, psychological treatment is often evaluated as if it were an antibiotic, with success implying improvements in symptoms and then durability of these changes when the treatment is withdrawn. This leads to the conclusion that if symptoms return following psychological treatment then the treatment has failed. This clearly is not the case – the treatment

did affect the symptoms, despite the lack of durability. However, this argument does suggest an alternative regimen i.e. that psychological treatments should also be provided as maintenance therapy given in a depot every few months. These assumptions about treatment mechanisms have seriously hindered the adoption of psychological treatments into health services, because although the maintenance component of the therapy will increase costs, there are likely to be further benefits in terms of quality of life for the patients.

References

1. Hemsley DR, Garety PA. The formation of maintenance of delusions: a Bayesian analysis. *Br J Psychiatry* 1986; 149: 51–6.
2. Chadwick PDJ, Birchwood MJ. The omnipotence of voices: a cognitive approach to hallucinations. *Br J Psychiatry* 1994; 164: 190–201.
3. Frith C, Done J. Positive symptoms of schizophrenia. *Br J Psychiatry* 1989; 154: 569–70.
4. Gelder M, Gath D, Mayou R. *The Oxford Textbook of Psychiatry*. Oxford University Press: Oxford, 1983.
5. Slade PD. The effects of systemic desensitization on auditory hallucinations. *Behav Res Ther* 1972; 10: 85–91.
6. Slade PD. The psychological investigation and treatment of auditory hallucinations: a second case report. *Br J Med Psychol* 1973; 46: 293–6.
7. Done D, Frith C, Owens DC. Reducing persistent auditory hallucinations through occlusion of monaural input. *Br J Clin Psychol* 1986; 25: 151–2.
8. Jones SR, Fernyhough C. Neural correlates of inner speech and auditory verbal hallucinations: A critical review and theoretical integration. *Clin Psychol Rev* 2007; 27: 140–54.
9. Fernyhough C. Alien voices and inner dialogue: Towards a developmental account of auditory verbal hallucinations. *New Ideas Psychol* 2004; 22: 29–68.
10. Birchwood M, Chadwick P. The omnipotence of voices: testing the validity of a cognitive model. *Psychol Med* 1997; 27: 1345–53.
11. Romme M, Escher S. *Accepting voices*. London: Mind Publications, 1993.
12. Wykes T, Hayward P, Thomas N et al. What are the effects of group cognitive behaviour therapy for voices? A randomized control trial. *Schizophr Res* 2005; 77: 201–10.
13. Liberman R, Telegan J, Patterson R, Baker V. Reducing delusional speech in chronic paranoid schizophrenics. *J Appl Behav Anal* 1973; 6: 57–64.
14. Watts FN, Powell GE, Austin SV. The modification of abnormal beliefs. *Br J Med Psychol* 1973; 46: 359–63.
15. Peters ER, Garety P. Cognitive functioning in delusions: A longitudinal analysis. *Behav Res Ther* 2006; 44: 481–514.
16. Peters ER, Day S, McKenna J, Orbach G. The incidence of delusional ideation in religious and psychotic populations. *Br J Clin Psychol* 1999; 38: 83–96.
17. Bentall RP, Kinderman P, Kaney S. The self, attributional processes and abnormal beliefs: towards a model of persecutory delusions. *Behav Res Ther* 1994; 33: 331–41.
18. Freeman D, Garety PA, Kuipers E et al. A cognitive model of persecutory delusions. *Br J Clin Psychol* 2002; 41: 331–347.
19. Beck AT. Successful outpatient psychotherapy of a chronic schizophrenic with a delusion based on borrowed guilt. *J Study Interpers Process* 1952; 15: 305–12.

20. Shapiro MB, Ravenette AT. A preliminary experiment on paranoid delusions. *J Ment Sci* 1959; 105: 295–312.
21. Fowler D, Garety P, Kuipers E. Cognitive therapy for psychosis: formulation, treatment, effects and service implications. *J Mental Health* 1998; 7: 123–33.
22. Cunningham-Owens DG, Carroll A, Fattah S et al. A randomised controlled trial of a brief educational package for schizophrenic out-patients. *Acta Psychiatr Scand* 2001;103: 362–9.
23. Tarrier N, Barrowclough C, Vaughn C et al. The community management of schizophrenia: a controlled trial of a behavioural intervention with families. *Br J Psychiatry* 1988; 153: 532–42.
24. Garety P, Kuipers E, Fowler D et al. A cognitive model of the positive symptoms of psychosis. *Psychol Med* 2001; 31: 189–95.
25. Morrison AP. The interpretation of intrusions in psychosis: An integrative cognitive approach to psychotic symptoms. *Behav Cognit Psychother* 2001; 29: 257–76.
26. Morrison AP. *A Casebook of Cognitive Therapy for Psychosis*. Hove, UK: Brunner-Routledge, 2002.
27. Kingdon D, Turkington D. *Cognitive therapy for schizophrenia*. New York: Guilford Press, 2005.
28. Tarrier N, Wykes T. Is there evidence that cognitive behaviour therapy is an effective treatment for schizophrenia? A cautious or cautionary tale? *Behav Res Ther* 2004; 42: 1377–1401.
29. Pilling S, Bebbington P, Kuipers E et al. Psychological treatments in schizophrenia: I Meta-analysis of family intervention and cognitive behaviour therapy. *Psychol Med* 2002; 32: 763–82.
30. Zimmermann G, Favrod J, Trieu VH, Ponini V. The effect of cognitive behavioral treatment on the positive symptoms of schizophrenia spectrum disorders: A meta-analysis. *Schizophr Res* 2005; 77: 1–9.
31. Lewis S, Tarrier N, Haddock G et al. Randomised controlled trial of cognitive-behavioural therapy in early schizophrenia: acute-phase outcomes. *Br J Psychiatry* 2002; 181: 91–7.
32. Valmaggia LR, van der Gaag M, Tarrier N et al. Cognitive-behavioral therapy for refractory psychotic symptoms of schizophrenia resistant to atypical antipsychotic medication. Randomised controlled trial. *Br J Psychiatry* 2005; 186: 324–30.
33. Tarrier N, Yusupoff L, Kinney C et al. A randomised controlled trial of intensive cognitive behaviour therapy for patients with chronic schizophrenia. *BMJ* 1998; 317: 303–7.
34. Tarrier N, Wittkowski A, Kinney C et al. The durability of the effects of cognitive behaviour therapy in the treatment of chronic schizophrenia: twelve months follow up. *Br J Psychiatry* 1999; 174: 500–4.
35. Kuipers E, Garety P, Fowler D et al. London-East Anglia randomised controlled trial of cognitive-behavioural therapy for psychosis: 1. Effects of the treatment phase. *Br J Psychiatry* 1997; 171: 319–27.
36. Kuipers E, Fowler D, Garety P et al. London-East Anglia randomised controlled trial of cognitive-behavioural therapy for psychosis: III. Follow-up and economic evaluation at 18 months. *Br J Psychiatry* 1998; 173: 61–8.
37. Sensky T, Turkington D, Kingdon D et al. A randomised controlled trial of cognitive-behavioral therapy for persistent symptoms in schizophrenia resistant to medication. *Arch Gen Psychiatry* 2000; 57: 165–72.
38. Turkington D, Kingdon D, Turner T, the Insight Group. Effectiveness of a brief cognitive behavioural therapy intervention in the treatment of schizophrenia. *Br J Psychiatry* 2002; 180: 523–8.

39. Turkington D, Kingdon D, Rathod S et al. Outcomes of an effectiveness trial of cognitive-behavioural intervention by mental health nurses in schizophrenia. *Br J Psychiatry* 2006; 189: 36–40.
40. Barrowclough C, Haddock G, Lobban F et al. Group cognitive-behavioural therapy for schizophrenia: randomised controlled trial. *Br J Psychiatry* 2006; 189: 527–32.
41. Trower P, Birchwood M, Meaden A et al. Cognitive therapy for command hallucinations: Randomised controlled trial. *Br J Psychiatry* 2004; 184: 312–20.
42. Startup M, Jackson MC, Evans KE, Bendix S. North Wales randomized controlled trial of cognitive behaviour therapy for acute schizophrenia spectrum disorders: two-year follow-up and economic evaluation. *Psychol Med* 2005; 35: 1307–16.
43. Chadwick P, Birchwood M. The omnipotence of voices: a cognitive approach to auditory hallucinations. *Br J Psychiatry* 1997; 164: 190–201.
44. Frith CD. *The cognitive neuropsychology of schizophrenia*. Hillside, NS: Lawrence Erlbaum, 1992.

Additional reading

Manuals outlining cognitive behavior therapy for psychosis

- Chadwick P, Birchwood M, Trower, P. *Cognitive Therapy for Delusions, Voices and Paranoia*. Chichester, UK: Wiley, 1996.
- Fowler D, Garety PA, Kuipers E. *Cognitive Behaviour Therapy for Psychosis: Theory and Practice*. Chichester, UK: Wiley, 1995.
- Kingdon D, Turkington D. *Cognitive Therapy of Schizophrenia*. New York: Guilford Press, 2005.
- Nelson H. *Cognitive Behaviour Therapy with Schizophrenia. A Practice Manual*. Cheltenham, UK: Stanley Thornes, 1997.

Clinical casebooks of cognitive behavior therapy for psychosis

- Kingdon D, Turkington D. *The Case Study Guide to Cognitive Behaviour Therapy of Psychosis*. Chichester, UK: Wiley, 2002.
- Morrison AP. *A Casebook of Cognitive Therapy for Psychosis*. Hove, UK: Brunner-Routledge, 2002.

Self-help resources

- Baker P. *The Voice Inside. A Practical Guide to Coping with Hearing Voices*. Manchester, UK: Hearing Voices, 2003.
- Freeman D, Freeman J, Garety P. *Overcoming Paranoid and Suspicious Thoughts*. London: Constable and Robinson, 2006.
- Romme M, Escher S. *Making Sense of Voices*. London: Mind Publications, 2000.

Management of negative symptoms

David L Copolov and David J Castle

As a common source of chronic disability, negative symptoms serve to remind clinicians of the imperfections of psychiatric therapeutics. Negative symptoms are conceptualized as those occurring as a result of a loss of function¹. They include affective flattening, poverty of speech (alogia), diminished drive, and loss of pleasure (anhedonia). They are present to varying degrees in patients with schizophrenia with recent estimates being that 15–25% of people with the disorder experience negative symptoms of sufficient severity to warrant symptom-targeted therapeutic intervention². When present to a such a degree, these symptoms often contribute to social dislocation and isolation and greatly reduced activities of daily living.

Just as there is a clear overlap between the positive and negative symptoms of schizophrenia in individual patients, so too the treatment for these two classes of symptoms overlaps – both involve pharmacotherapy, supportive psychotherapy, and attention to broader psychosocial issues such as employment, accommodation, and interactions with others (see also Chapters 11 and 12). But in dealing with negative symptoms, special emphasis is placed on the consideration of differential diagnoses and on the use of psychosocial rehabilitation strategies.

Negative symptoms are often present from the onset of schizophrenia³ but are approximately half as common in early phase patients compared with more chronic ones⁴. These symptoms respond to an extent to treatment, but less definitively than positive symptoms⁵. It is instructive to subcategorize negative symptoms into phasic symptoms that improve in tandem with positive symptoms; and enduring symptoms. The latter appear to correlate with poor premorbid function, more severe global psychopathology and impaired neuropsychological performance⁶. Such enduring negative symptoms are evident even in first episode psychoses⁷.

Diagnosis before treatment

There are several important causes of emotional withdrawal, avolition, reduced spontaneity, and reduced affective range in patients with schizophrenia other than the underlying disease processes^{3,8,9} (Box 3.1).

One such secondary cause is that of negative symptoms secondary to positive psychotic symptoms. Hallucinations and delusions may lead to emotional and social withdrawal both as a response to the often threatening content of these psychotic phenomena, and to the attempt to reduce external stimuli in the face of being overwhelmed by emotional experiences. During acute psychotic episodes it may be impossible to distinguish between secondary negative symptoms originating from this cause and primary negative symptoms; such a distinction may be possible only in retrospect.

Negative symptoms due to the extrapyramidal side-effects (EPSE) of antipsychotic drugs were more common as differential diagnoses with the older generation of antipsychotic drugs (see Chapter 1). But even with atypical drugs in current use, only clozapine and quetiapine carry a very low risk of EPSE¹⁰, so this is still an important differential diagnosis to consider. The most obvious feature shared by primary negative symptoms and extrapyramidal syndromes is diminished spontaneous movements (bradykinesia)⁸. Differentiating features therefore focus on the non-bradykinetic set of EPSE symptoms and signs including akathisia, tremor, and rigidity. These should be considered when assessing the likelihood that a particular antipsychotic drug might be causing EPSE.

The features of comorbid depression that overlap with primary negative symptoms include depressed affect, a reduced capacity for pleasure, and decreased engagement with others. Clarification of the differential diagnosis

Box 3.1 Differential diagnoses of negative symptoms.

1. **Primary negative symptoms**
due to underlying disease processes
2. **Secondary negative symptoms**
secondary to positive psychotic symptoms
secondary to extrapyramidal side-effects of antipsychotic drugs
secondary to depression
secondary to catatonia

is aided by a detailed consideration of the patient's mood and an enquiry into possible accompanying depressive symptoms such as recurrent suicidal ideation, persistent insomnia, significant weight loss, and intrusive feelings of worthlessness (see Chapter 5). Although there are similarities between flat-tended and depressed affect, in terms of reduced mobility and range, several studies¹¹ have shown that the distinction between these two abnormalities of affect can usually be made reliably, assisted by differentiating features such as tearfulness and observed sadness.

Although catatonia is relatively rare in developed countries, it still needs to be kept in mind as a cause of the type of psychomotor inhibition that can be confused with primary negative symptoms¹². Distinguishing features of catatonia include stupor, bizarre posturing, negativism, and waxy flexibility.

Management of negative symptoms

Negative symptoms warrant particular attention from clinicians because they generally fail to give rise to appropriate levels of concern from patients – instead they tend to engender an attitude of relative indifference¹³. Thus clinicians must rely on appropriate and directed history taking, discussion with family members or others who know the patient well, and observation to diagnose and track these symptoms.

The philosophy underlying the diagnosis and treatment of negative symptoms must take into account the fact that in some circumstances it may not be possible to distinguish between primary and secondary negative symptoms. Under such circumstances it may be necessary to treat potentially reversible causes of the negative symptoms, such as depression or EPSE, if there is a reasonable level of suspicion that such causes might be relevant to the patient's presentation. When improvement occurs in the context of uncertainty about the extent to which the treatment has affected primary or secondary negative symptoms, there is a possibility that a 'pseudospecific' response has been elicited². Although this may muddy the waters in terms of mechanisms of action, in practical terms the key issue is that the patient improves.

Prevention and management of secondary negative symptoms

The principles underlying the treatment of the positive symptoms of schizophrenia are outlined elsewhere in this book (see Chapters 1 and 2). Treatment of

these symptoms will usually result in improvements in negative symptoms as a result of either 'en bloc' improvements in the symptoms of the disorder (with negative symptoms typically improving to a lesser extent than positive symptoms)¹⁴ or improvements in the negative symptoms that are more directly the consequence of positive ones. One key element of such treatment is the use of antipsychotic drugs. In order to reduce the likelihood of EPSE arising during the course of treatment with such drugs, the best approach is to choose a second generation antipsychotic medication such as quetiapine, olanzapine, aripiprazole, ziprasidone, or lower dose risperidone (Box 3.2). It must be remembered, however, that the risk of EPSE is not uniform across this range of drugs¹⁰.

If financial considerations preclude the use of newer drugs, conventional antipsychotic drugs should be used at the lowest effective dose. For haloperidol this dose is likely to be in the range of 3–4 mg/day¹⁵ or 4–6 mg/day¹⁶; doses which are high enough to achieve the 65% or higher dopamine D2 receptor occupancy levels required for antipsychotic efficacy^{17–19}.

The trend towards lower antipsychotic dosages is a welcome development but it must be recognized that increasing drug doses may need to be used in order to obtain adequate therapeutic responses. Several groups have shown that doses in the 200–500 mg chlorpromazine equivalents (CPZ eq)/day range are required in order to provide reasonable response rates and that treatment responsiveness plateaus definitively in the 500–800 mg CPZ eq/day range²⁰. Doses in this latter range are, however, associated with much higher rates of EPSE; thus, it has been estimated that to benefit one additional patient in terms of efficacy by treating with these higher doses will cause significant EPSE in up to four patients in the first 6 months of maintenance therapy²⁰.

Observations such as these have two corollaries. First, there is no fixed 'low dose that fits all' for each antipsychotic drug, and dose response relationships need to be determined for each patient. Second, there are doses below which a significant proportion of patients do not respond. For example, in a study

Box 3.2 Treatment approaches aimed at minimizing extrapyramidal side-effects.

Use of newer generation drugs if possible
 Lowest effective dose of antipsychotic drugs
 Judicious use of anticholinergic medications

of standard versus low dose fluphenazine decanoate (12.5–50 mg every 2 weeks versus 1.25–5 mg every 2 weeks), relapse rates over 9 months were eight times higher (56% versus 7%) in the lower dose group²¹. Similarly, studies with risperidone have shown that while there is a recommendation to start this drug at 2 mg/day²² efficacy is considered to be greatest in the 4–6 mg range; below 2 mg/day, the drug is generally ineffective in non-elderly adults²³.

The fact that a substantial number of patients on conventional antipsychotic drugs (ranging from 20 to 66%²⁴) experience extrapyramidal symptoms may therefore be seen as a calculated trade-off of side-effects for treatment response. Nevertheless, there is also a high rate of failure to recognize EPSE²⁵, so vigilance regarding these side-effects should always be maintained. If EPSE are detected, either a judicious lowering of the dose to a level sufficient to maintain efficacy, switching to a drug with less EPSE-causing potential²⁶, or the addition of anticholinergic drugs such as benztropine²⁷ should be considered (see Chapter 1). Because of side-effects such as dry mouth, blurred vision, constipation, tachycardia, and urinary hesitancy, the prophylactic use of anticholinergic agents should be reserved for those being treated with conventional antipsychotic drugs with a history of EPSE, especially those in whom EPSE have led to the discontinuation of antipsychotic medications²⁸.

The third significant cause of secondary negative symptoms in schizophrenia is depression. The treatment of depression in schizophrenia is discussed in Chapter 5.

Treatment of primary negative symptoms

There are two elements in treating primary negative symptoms – choosing the most efficacious antipsychotic drug and instigating appropriate psychosocial interventions.

Several reports have claimed efficacy for treating primary negative symptoms with atypical antipsychotic drugs including amisulpride alone^{29–32}, amisulpride as an adjunct to haloperidol³³, or clozapine³⁴; olanzapine³⁵; risperidone³⁶; and clozapine alone^{37,38}. Some of these studies have employed path analysis – a statistical technique that factors out the causes of secondary negative symptoms, including EPSE, depression, and positive symptoms. Overall the efficacy of available antipsychotic drugs on negative symptoms^{39–42} is modest, inconsistent, and often of marginal clinical value. There is some suggestive, but far from unequivocal, evidence that newer generation (atypical) antipsychotic drugs have a preferential effect on primary negative

symptoms and should therefore be considered first line treatments when wishing to reduce the likelihood of these symptoms occurring, or treating those in whom these symptoms are prominent. This is compatible with the treatment algorithm outlined in Chapter 1. It should be noted, though, that very few studies have addressed treatment response in patients with the so-called deficit syndrome, in which negative symptoms predominate.

Other pharmacological approaches to negative symptoms have included the adjunctive use of glycine⁴³, D-cycloserine^{44,45}, fluvoxamine⁴⁶, deprenyl⁴⁷, mirtazapine⁴⁸, galantamine⁴⁹, and pergolide⁵⁰. These approaches have yet to be validated.

Psychosocial aspects of managing negative symptoms

A subcomponent meta-analysis and review of 24 psychosocial intervention studies in which negative symptoms had been assessed, demonstrated a greater beneficial effect of such therapies on negative than on positive symptoms⁵¹. On the basis of chronic patients responding to such treatments better than acute patients, this review also suggested that clinicians adopt a 'phase of illness' orientation to treatment priorities, with priority being given to optimizing medication in the acute phase, and to optimizing psychosocial treatments in the chronic phase.

Environmental understimulation is one psychosocial factor that has been shown to exacerbate negative symptoms and is susceptible to intervention. Although research in long-stay psychiatric institutions demonstrates the deleterious role of environmental understimulation in inpatient settings^{52,53}, it is just as important to keep track of this factor in the community settings in which patients are now usually treated. The elements comprising environmental understimulation include:

- having little contact with the outside world;
- having little or no engagement in a constructive occupation; and
- spending long periods of time doing nothing.

It has been shown that the introduction of measures to address these issues brings substantial benefits⁵² in terms of negative symptoms reduction, without a concomitant increase in positive symptoms. In a study of the post-discharge fate of patients who had been previously long-stay⁵⁴, it has been

shown that the provision of enriched social environments is associated with a lessening of negative symptoms, but it may take a number of years for this effect to become evident. Elements that appear to be relevant to improvements in negative symptom status include increases in the number of friends, increased contact with those in the community providing services and goods (such as local shopkeepers), and the provision of less restrictive living environments.

Many of the psychosocial treatments and strategies which are valuable in the management of schizophrenia, such as case management, occupational therapy, assertive community treatment, and vocational rehabilitation (see Chapters 11, 12, and 17) attempt to address the negative impact of environmental understimulation on patients. Specific psychosocial interventions that have recently been shown to have some effect on negative symptoms include social skills training⁵⁵, group therapy involving multiple families⁵⁶, cognitive remediation therapy⁵⁷, and cognitive behavior therapy^{58–60}. The cognitive behavior therapy of negative symptoms aims to harness motivation and promote social and emotional re-engagement by techniques including behavioral self-monitoring, activity scheduling, and graded task assignments⁶¹.

It is important to note the iterative relationship between psychosocial treatments and pharmacotherapy. Antipsychotic medication, such as clozapine, facilitates patient engagement in psychosocial rehabilitation programs. In turn these programs, when used adjunctively with pharmacotherapy, but often only after a period of several months, result in additional symptom improvement and better quality of life⁶².

Negative symptoms and family members

It is imperative to recognize and help deal with the impact of schizophrenia on family members in the post-deinstitutionalization era which sees them as the principal caregivers for adults with major psychiatric disorders (see Chapter 14). Family members are often more distressed by the effects of negative symptoms than are patients themselves^{63,64}. This is especially the case when family members have inadequate knowledge about schizophrenia and perceive the symptoms to be under the patient's control⁶⁵.

Whether individually or in group settings⁵⁶, family members can be helped to cope with negative symptoms in their loved ones⁶³. Psychoeducation aimed at clarifying that these symptoms are not the patient's fault is important.

Blunted affect may lead to a misreading of the patient's level of interest in activities – so relatives should be advised to ask judiciously about the patient's feelings, rather than assume that impassive facial expressions mean that interest is lacking. One strategy to deal with poverty of speech may be to arrange joint activities outside the home. This lessens the pressure on conversation and may provide topics for later discourse. When engaging in discussion, relatives should be encouraging but not place high expectations on what patients can contribute; they should learn to be tolerant of long pauses in conversation and to be active in filling in some of the silences with undemanding contributions. Relatives can help patients with reduced drive by regularly scheduling enjoyable recreational activities and making a special effort to include them in family activities.

Conclusions

Negative symptoms are a major contributor to the poor quality of life experienced by patients with schizophrenia^{66,67}. While there is a clear need to undertake more research into the pathopsychology of these symptoms in order to improve the limited therapeutic interventions currently available^{39,42,68}, there are practical and proven steps that clinicians can take to assist patients deal with secondary, and to a lesser extent, primary negative symptoms.

References

1. Andreasen NC, Flaum M, Swayze II VW et al. Positive and negative symptoms in schizophrenia. A critical reappraisal. *Arch Gen Psychiatry* 1990; 47: 615–21.
2. Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR. The NIMH-MATRICES Consensus Statement on Negative Symptoms. *Schizophr Bull* 2006; 32: 214–19.
3. Peralta V, Cuesta MJ, Martinez-Larrea A, Serrano JF. Differentiating primary from secondary negative symptoms in schizophrenia: a study of neuroleptic-naïve patients before and after treatment. *Am J Psychiatry* 2000; 157: 1461–6.
4. Ventura J, Nuechterlein KH, Green MF et al. The timing of negative symptom exacerbations in relationship to positive symptom exacerbations in the early course of schizophrenia. *Schizophr Res* 2004; 69: 333–42.
5. Arndt S, Andreasen NC, Flaum M et al. A longitudinal study of symptom dimensions in schizophrenia: prediction and patterns of change. *JAMA* 1995; 272: 352–60.
6. Tandon R, DeQuardo JR, Taylor SF et al. Phasic and enduring negative symptoms in schizophrenia: biological markers and relationship to outcome. *Schizophr Res* 2000; 45: 191–201.
7. Edwards J, McGorry PD, Waddell FM, Harrigan SM. Enduring negative symptoms in first-episode psychosis: comparison of six methods using follow-up data. *Schizophr Res* 1999; 40: 147–58.
8. Barnes TRE. Issues in the clinical assessment of negative symptoms. *Curr Opin Psychiatry* 1994; 7: 35–8.

9. Buchanan RW, Gold JM. Negative symptoms: diagnosis, treatment and prognosis. *Int Clin Psychopharmacol* 1996; 11 (Suppl 2): 3–11.
10. Weiden PH. EPSE Profiles: the atypical antipsychotics are not all the same. *J Psychiatr Pract* 2007; 13: 1.
11. Newcomer JW, Faustman WO, Yeh W, Csernansky JG. Distinguishing depression and negative symptoms in unmedicated patients with schizophrenia. *Psychiatr Res* 1990; 31: 243–50.
12. Peralta V, Cuesta MJ. Negative, parkinsonian, depressive and catatonic symptoms in schizophrenia: a conflict of paradigms revisited. *Schizophr Res* 1999; 40: 245–53.
13. Seltén J-P, Wiersma D, van den Bosch RJ. Distress attributed to negative symptoms in schizophrenia. *Schizophr Bull* 2000; 26: 737–44.
14. Meltzer H, Kostakaglu E, Lee M. Response: negative symptoms redux. *Neuropsychopharmacology* 2000; 22: 642–3.
15. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia. *Arch Gen Psychiatry* 1991; 48: 739–45.
16. Nordstrom AL, Farde I, Wiesel FA et al. Central D₂-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. *Biol Psychiatry* 1993; 33: 227–35.
17. Farde L, Nordstrom AL, Wiesel FA et al. Positron emission tomographic analysis of central D₁ and D₂ dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: relation to extrapyramidal side effects. *Arch Gen Psychiatry* 1992; 49: 538–44.
18. Kapur S, Zipursky R, Roy P et al. The relationship between D₂ receptor occupancy and plasma levels on low dose oral haloperidol: a PET study. *Psychopharmacology (Berlin)* 1997; 131: 148–52.
19. Kapur S, Zipursky R, Jones C et al. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry* 2000; 157: 514–20.
20. Mossman D. A decision analysis approach to neuroleptic dosing: insights from a mathematical model. *J Clin Psychiatry* 1997; 58: 66–72.
21. Kane JM, Rifkin A, Woerner M et al. Low-dose neuroleptic treatment of outpatient schizophrenics. I. Preliminary results for relapse rates. *Arch Gen Psychiatry* 1983; 40: 893–6.
22. MIMS Annual Australia. CMP Medica Sydney, Australia 2006.
23. Williams R. Optimal dosing with risperidone: updated recommendations. *J Clin Psychiatry* 2001; 62: 4.
24. Muscettola G, Barbato G, Pampallona S et al. Extrapyramidal syndromes in neuroleptic-treated patients: prevalence, risk factors, and association with tardive dyskinesia. *J Clin Psychopharmacol* 1999; 19: 203–8.
25. Weiden PJ, Shaw E, Mann J. Causes of neuroleptic non-compliance. *Psychiatr Ann* 1986; 16: 571–8.
26. Weiden PJ, Aquila R, Dalheim L, Standard JM. Switching antipsychotic medications. *J Clin Psychiatry* 1997; 58 (Suppl 10): 63–72.
27. Holloman LC, Marder SR. Management of acute extrapyramidal effects induced by antipsychotic drugs. *Am J Health Syst Pharm* 1997; 54: 2461–77.
28. Lehman AF, Steinwachs DM, Dixon LB et al. Translating research into practice: the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. *Schizophr Bull* 1998; 24: 1–10.
29. Boyer P, Lecrubier Y, Puech AJ et al. Treatment of negative symptoms in schizophrenia with amisulpride. *Br J Psychiatry* 1995; 166: 68–72.
30. Paillere-Martinot ML, Lecrubier Y, Martinot JL, Aubin F. Improvement of some schizophrenic deficit symptoms with low doses of amisulpride. *Am J Psychiatry* 1995; 152: 130–4.

31. Loo H, Poirier-Littre MF, Theron M et al. Amisulpride versus placebo in the medium-term treatment of the negative symptoms of schizophrenia. *Br J Psychiatry* 1997; 170: 18–22.
32. Danion JM, Rein W, Fleurol O. Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. *Am J Psychiatry* 1999; 156: 610–16.
33. Bogetto F, Fonzo V, Maina G, Ravizza I. Adjunctive fluoxetine or amisulpride improves schizophrenic negative symptoms. *Eur J Psychiatry* 1995; 9: 119–27.
34. Munro J, Matthiasson P, Osborne S et al. Amisulpride augmentation of clozapine: an open non-randomized study in patients with schizophrenia partially responsive to clozapine. *Acta Psychiatr Scand* 2004; 110: 292–8.
35. Tollefson GD, Sanger TM. Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. *Am J Psychiatry* 1997; 154: 466–74.
36. Moller JH, Muller H, Borison RL et al. A path-analytical approach to differentiate between direct and indirect drug effects on negative symptoms in schizophrenic patients. A re-evaluation of the North American risperidone study. *Eur Arch Psychiatr Clin Neurosci* 1996; 245: 45–9.
37. Meltzer HY. Dimensions of outcome with clozapine. *Br J Psychiatry* 1992; (Suppl): 46–53.
38. Brar JS, Chengappa R, Parpcally H et al. The effects of clozapine on negative symptoms in patients with schizophrenia with minimal positive symptoms. *Ann Clin Psychiatry* 1997; 9: 227–34.
39. Erhart SM, Marder SR, Carpenter WT. Treatment of schizophrenia negative symptoms: future prospects. *Schizophr Bull* 2006; 32: 234–3.
40. McEvoy JP, Lieberman JA, Stroup TS. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 2006; 163: 600–10.
41. Murphy BP, Chung YC, Park TW, McGorry PD. Pharmacological treatment of primary negative symptoms in schizophrenia: a systematic review. *Schizophr Res* 2006; 88:5–25.
42. Buckley PF, Stahl SM. Pharmacological treatment of negative symptoms of schizophrenia: therapeutic opportunity or cul-de-sac? *Acta Psychiatr Scand* 2007; 115: 93–100.
43. Heresco-Levy U, Javitt DC, Ermilov M et al. Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. *Arch Gen Psychiatry* 1999; 56: 29–36.
44. Goff DC, Tsai G, Levitt J et al. A placebo-controlled trial of D-cycloserine added to conventional neuroleptics in patients with schizophrenia. *Arch Gen Psychiatry* 1999; 56: 21–7.
45. Heresco-Levy U, Ermilov M, Shimoni J et al. Placebo-controlled trial of D-cycloserine added to conventional neuroleptics, olanzapine, or risperidone in schizophrenia. *Am J Psychiatry* 2002; 159: 480–2.
46. Silver H, Shmugliakov N. Augmentation with fluvoxamine but not maprotiline improves negative symptoms in treated schizophrenia: evidence for a specific serotonergic effect from a double-blind study. *J Clin Psychopharmacol* 1998; 18: 208–11.
47. Jungerman T, Rabinowitz D, Klein E. Deprenyl augmentation for treating negative symptoms of schizophrenia: a double-blind controlled study. *J Clin Psychopharmacol* 1999; 19: 522–5.
48. Berk M, Ichim C, Brook S. Efficacy of mirtazapine add on therapy to haloperidol in the treatment of the negative symptoms of schizophrenia: a double-blind randomized placebo-controlled study. *Int J Clin Psychopharmacol* 2001; 16: 87–92.

49. Rosse RB, Deutsch SI. Adjuvant galantamine administration improves negative symptoms in a patient with treatment-refractory schizophrenia. *Clin Neuropharmacol* 2002; 25: 272–5.
50. Roesch-Ely D, Gohring K, Gruschka P et al. Pergolide as adjuvant therapy to amisulpride in the treatment of negative and depressive symptoms in schizophrenia. *Pharmacopsychiatry* 2006; 39: 115–16.
51. Mojtabai R, Nicholson RA, Carpenter BN. Role of psychosocial treatments in management of schizophrenia: a meta-analytic review of controlled outcome studies. *Schizophr Bull* 1998; 24: 569–87.
52. Wing JK, Brown GW. *Institutionalism and Schizophrenia*. Cambridge University Press, Cambridge, UK, 1970.
53. Oshima I, Mino Y, Inomata Y. Effects of environmental deprivation on negative symptoms of schizophrenia: a nationwide survey in Japan's psychiatric hospitals. *Psychiatr Res* 2006; 136: 163–71.
54. Leff J, Thornicroft G, Coxhead N, Crawford C. The TAPS Project 22: a five-year follow-up of long-stay psychiatric patients discharged to the community. *Br J Psychiatry* 1994; 165 (Suppl 25): 13–17.
55. Kopelowicz A, Liberman RP, Mintz J, Zarate R. Comparison of efficacy of social skills training for deficit and nondeficit negative symptoms in schizophrenia. *Am J Psychiatry* 1997; 154: 424–5.
56. Dyck DG, Short RA, Hendryx MS et al. Management of negative symptoms among patients with schizophrenia attending multiple-family groups. *Psychiatr Serv* 2000; 51: 513–19.
57. Wykes T, Reeder C, Corner J et al. The effects of neurocognitive remediation on executive processing in patients with schizophrenia. *Schizophr Bull* 1999; 25: 291–308.
58. Sensky T, Turkington D, Kingdon D. A randomized controlled trial of cognitive-behavioral therapy for persistent symptoms in schizophrenia resistant to medication. *Arch Gen Psychiatry* 2000; 57: 165–72.
59. Rector NA, Beck AT. Cognitive behavioral therapy for schizophrenia: an empirical review. *J Nerv Ment Dis* 2001; 189: 278–87.
60. Rector NA, Seeman MV, Segal ZV. Cognitive therapy of schizophrenia: a preliminary randomized controlled trial. *Schizophr Res* 2003; 63: 1–11.
61. Rector NA, Beck AT. Cognitive behavioral therapy for schizophrenia: from conceptualization to intervention. *Can J Psychiatry* 2002; 47: 39–48.
62. Rosenheck R, Tekell J, Peters J et al for the Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. Does participation in psychosocial treatment augment the benefit of clozapine? *Arch Gen Psychiatry* 1998; 55: 618–25.
63. Mueser KT, Gingerich S. *Coping with Schizophrenia: A Guide for Families*. Oakland, CA: New Harbinger Publications, 1994.
64. Provencher HL, Mueser KT. Positive and negative symptom behaviors and caregiver burden in the relatives of persons with schizophrenia. *Schizophr Res* 1997; 26: 71–80.
65. Harrison C, Dadda M, Smith G. Family caregivers' criticism of patients with schizophrenia. *Psychiatr Serv* 1998; 49: 918–24.
66. Mueser KT, Douglas MS, Bellack AS, Morrison RL. Assessment of enduring deficit and negative symptom subtypes in schizophrenia. *Schizophr Bull* 1991; 17: 565–82.
67. Bow-Thomas CC, Velligan DI, Miller AL, Olsen J. Predicting quality of life from symptomatology in schizophrenia at exacerbation and stabilization. *Psychiatry Res* 1999; 86: 131–42.
68. Carpenter WT Jr, Arango C, Buchanan RW, Kirkpatrick B. Deficit psychopathology and a paradigm shift in schizophrenia research. *Soc Biol Psychiatry* 1999; 46: 352–60.

Cognitive dysfunction in schizophrenia

Til Wykes and David J Castle

Cognitive difficulties have been an integral part of the diagnosis of schizophrenia in all diagnostic systems beginning with Kraepelin and Bleuler more than 100 ago, although they differed on the specific mechanism that was at fault; thus, Bleuler stressed the loosening of the associational threads that tie thoughts together, whilst Kraepelin and others emphasized poor attention and memory difficulties. This chapter describes these difficulties, with particular reference to the effect they have on quality of life and life choices. Treatment options for cognitive difficulties in schizophrenia are relatively new and have not had their full potential developed. However, some detail on the most promising of the current therapeutic approaches is provided.

What cognitive systems are disturbed in schizophrenia?

Impairments are found in a wide range of cognitive systems in people with schizophrenia, but the severity of the impairment differs between systems. For instance, mild impairments are found in overall intelligence quotient (IQ), and on some perceptual tasks; moderate impairments are found on tasks that assess distractibility, delayed recall, and working memory; and severe impairments occur in the ability to manipulate information, sometimes called executive functioning (Table 4.1). People with schizophrenia are also often very slow in their responses and find it difficult to access a wide vocabulary. There is a distribution of these difficulties within the population of people with schizophrenia with the most severely disabled patients sometimes performing well below average. Of those people who continue to be involved with the

Table 4.1 A profile of cognitive deficits in schizophrenia

<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>
Perceptual skills	Distractability	Executive functioning
Delayed recognition memory	Memory and working memory	Verbal fluency
Verbal and full scale IQ	Delayed recall	Motor speed

psychiatric services, 85% perform below normal on one or more cognitive domains¹. In a normal population only 5% have such low levels of functioning, so cognitive deficits can be considered as a core feature of schizophrenia. However, it must be stressed that many people with schizophrenia fall within the normal range of cognitive functioning.

The profile of cognitive deficits found in people with schizophrenia is different to that found in patients with Alzheimer dementia. For example, Alzheimer sufferers have severe impairments in recognition memory but people with schizophrenia are only mildly impaired on these tasks. However, there seems to be only quantitative differences between those with a diagnosis of schizophrenia and those with either bipolar disorder or delusional disorder, with schizophrenia patients being the most disabled.

There has been considerable debate about whether these cognitive difficulties are static or progressive. Studies of birth cohorts or population studies have produced evidence that leaves little doubt about the existence of cognitive difficulties prior to the onset of the disorder. For example, Cannon et al² in a birth cohort from Dunedin, New Zealand, showed that cognitive difficulties at all developmental stages were predictive of the later development of a schizophrenia spectrum disorder (SSD) when compared with those who later developed other psychiatric disorders or none at all. Lewis et al³ also showed, in a cohort of Swedish military, that those who later developed schizophrenia were more likely to have low IQs than those who did not develop the disorder. More recently, Reichenberg et al⁴ replicated these results in a study of 54 000 17-year-old Israeli conscripts who were followed up for up to 11 years. They also found that the risk for SSDs increased with decreasing IQ score. Only poorer non-verbal reasoning conferred a significant increased risk for SSD after taking into account general intellectual ability. Because these data were all collected some time before the onset of the disorder the results are unlikely to be due to the prodrome phase of the illness.

It is also clear that there is a substantial worsening of cognitive performance with the onset of the disorder. Some of the deficits seem to be related to the presence of other symptoms (such as delusions), and remit as symptoms resolve. However, mild difficulties that were evident before the first episode can worsen into a severe cognitive deficit in the months before and during the first episode, and remain relatively stable after remission. For example, memory deficits that may have been mild prior to onset can become more severe and impede all kinds of learning and adaptation to new environmental challenges⁵.

Data from cross-sectional studies do not indicate many differences in cognitive functioning between:

- young patients with a short duration of illness, old patients with a short duration of illness, and old patients with a long duration of illness⁶;
- adolescent and chronic patients⁷;
- first episode patients and chronic patients^{8,9}.

These data suggest a relative stability of cognitive difficulties over time.

What are the effects of cognitive difficulties on symptoms, rehabilitation, and life skills?

Symptoms

It is tempting to assume that cognitive difficulties in schizophrenia are strongly correlated with positive symptoms (hallucinations and delusions), but studies tend to show that cognitive dysfunction accounts for only a small amount of variance in those symptoms^{10,11}. What is clear from high-risk and birth cohort studies is that cognitive difficulties themselves may play a causal role in the propensity for positive symptoms. However, we cannot yet distinguish within the group of people with schizophrenia the cognitive difficulties that may underpin the severity of specific symptoms. This is in part due to the lack of subtlety in the measurement of the symptoms themselves. Furthermore, the effect of a cognitive difficulty may only manifest if the cognitive system is stressed so that subtle difficulties, which can be compensated for under normal circumstances, break down. The experiment depicted in Figure 4.1, based on the proposal by Frith¹³ that difficulties in the ability to self-monitor may underlie the experience of hallucinations, demonstrates this. Thus, when asked to distinguish words spoken by themselves or others when they were fed back with distortion of the sound, people with

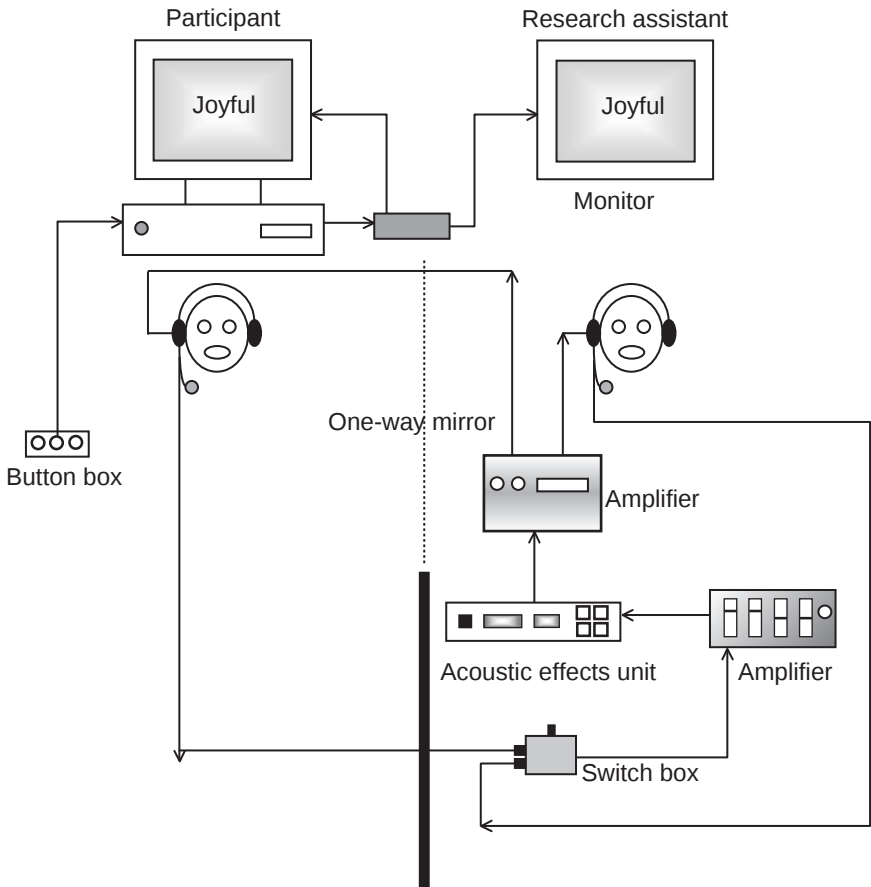


Figure 4.1 *The self monitoring of voices – the effects of distortion. From reference 13. Participant says ‘joyful’ and either hears their voice distorted or the voice of another person which is distorted. The task is to decide whether it the participant’s own voice or another. Patients who hear voices are biased to think that their own voice is an alien one.*

schizophrenia had many more problems in distinguishing their own voice and were biased to say it was someone else’s. This difficulty was measurable only when the words were distorted before feeding them back to the patient¹².

Rehabilitation

The presence of cognitive difficulties is related to the degree of dependence on psychiatric services, with higher levels of problems being associated with

more restrictive forms of care and a lack of independence. The difficulties are also predictive of future care. In a 6-year follow-up study of people who were moved into the community following the closure of a large psychiatric hospital, cognitive difficulties were a significant predictor of how much care a person would require, such that those with the least impairment were most able to live independently¹⁴. Perhaps most importantly, cognitive difficulties also predict the amount of care people are likely to receive. In an innovative study investigating the effects of cognitive impairments on the cost of care Patel et al¹⁵ showed that the overall level of cognitive difficulties led directly to the costs of care. Cognitive difficulties also predict levels of social performance. But perhaps more importantly, cognitive difficulties such as verbal memory problems appear to limit the amount that a person can learn from a traditional rehabilitation program. Thus, those people with the worst memories achieve the least improvement, particularly in terms of social skills.

Life skills

Cognitive difficulties not only make a difference to the level of care received, but also serve to limit the vocational rehabilitation potential of patients with schizophrenia. Bell et al¹⁶ have shown that cognition rather than symptoms seems to predict improvements in work quality following a 6-month rehabilitation program. Gold et al¹⁷ have also shown that the chance of gaining competitive paid employment following a rehabilitation program was affected by IQ, memory, and speed of processing information. But it must be emphasized that even the most severely cognitively disabled can work if they are provided with the right sort of job and effective supports (see Chapter 11). Several authors recently have discussed the relationship between cognition and overall functioning outcome¹⁸, showing the difficulties in making any assessment due to overall measurement problems. However, confirmatory path analyses revealed that neuropsychological performance predicts an intervening variable, functional capacity as measured using a controlled performance measure, and that this capacity measure then predicted overall functioning¹⁹.

Treatment issues

Even though the data suggest that cognitive dysfunctions in schizophrenia tend to be static over time, this does not mean that they are immutable. Indeed, there have been several recent innovative treatment approaches that have now instilled a degree of therapeutic optimism; these are outlined below.

What we have also learnt is that some interactions between treatments and cognitive difficulties can make matters worse. For example, when schizophrenia patients with high levels of cognitive difficulties were moved into community placements and had to increase their decision-making, their levels of positive symptoms worsened. In contrast, those without severe cognitive difficulty both improved their social behavior and showed a reduction in symptoms²⁰. It is therefore essential to take into account the current cognitive state of the person when determining treatment plans.

Pharmacological approaches to improving cognition in schizophrenia

Before considering the potential role of medications in ameliorating cognitive deficits in schizophrenia, it is as well to consider how medications might actually worsen cognitive ability. Thus, two of the drugs commonly used for schizophrenia patients, namely typical antipsychotics and anticholinergic agents, are known to impair cognition²¹. It is important to rationalize the use of such medications and avoid adding to the cognitive impairments that affect so many people with schizophrenia.

In terms of medications that might have a therapeutic effect for cognition in schizophrenia, it is the atypical antipsychotics that have attracted most recent attention. Early reports of an apparent amelioration of cognitive impairment were largely non-randomized within-group switch studies, where patients were assessed prior to, and after, switching from a typical to an atypical agent. Such a design is flawed in that there is no control for time variables and practice effects, nor for the effect of simply having withdrawn the typical agent. However, recent randomized control trials appear to support the notion that atypicals do exert some beneficial effect for cognition, at least relative to typicals²². One potential confounding effect in the comparison of typicals and atypicals is the lower rate of extrapyramidal side-effects (EPSE) with the latter; this would be most marked for tasks requiring manual dexterity. However, it seems that reduced EPSE, even with low dosing of the typical comparator, cannot account for all of the beneficial effect of the atypicals^{23,24}.

What has not been established is the effect of dosage and the time required to establish a positive effect on cognition with atypical antipsychotics. It is also unclear whether particular drugs have effects on particular domains of functioning. For example, it appears that clozapine improves attention and verbal fluency, but has much more equivocal effects on working memory^{25,26}.

Furthermore, the effect size of improvement in cognition with atypicals is relatively modest, and certainly does not compensate for the deficits found in many schizophrenia patients²³. Put statistically, the extent of improvement in any cognitive domain with the atypical agents is less than 0.5 of a standard deviation, whilst the extent of abnormality (see above) is of the order of two standard deviations from the normal population mean²⁷. Thus, whilst of enormous potential importance, the apparent cognitive benefits of the atypical antipsychotics require a great deal of further careful investigation, and do not obviate the need for other strategies such as psychological approaches. These partnership approaches, particularly cognitive remediation plus medication seem to produce larger effect sizes that may be clinically significant^{28,29}.

Other pharmacological approaches to enhancing cognition in schizophrenia include the addition of nicotine or psychostimulant drugs. Both of these strategies have shown some promise in enhancing certain cognitive domains, notably attention^{30,31}. However, many of the likely enhancement medications have not yet been supported in randomized controlled trials. Further work is required to validate any of these new approaches, and establish a role, if any, in clinical practice.

Psychological approaches

Psychological approaches to dealing with cognitive dysfunction in schizophrenia can be divided into three main categories.

- Direct approaches where the cognitive difficulty is the target of the rehabilitation.
- Changing the rehabilitation program so that it plays to the strengths rather than weaknesses of the patient.
- Changing the environment so that it compensates for the cognitive deficits.

Directly changing cognition

This approach is relatively new and various therapeutic techniques have been adopted directly to change or improve particular cognitive systems. Most have not been very effective but a few have shown improvements that have endured. The large number of non-effective studies has also provided guidance on what not to do. For example, we now know that only paying

people to improve their performance, simply practising a task over and over, or merely simplifying the task, is ineffective³².

The most robustly effective approach is called cognitive remediation therapy (CRT)^{32,33}. This therapy does not simply teach tasks, but concentrates on providing strategies for dealing with problems in general. What seems to be essential is to provide tasks where patients learn to achieve goals through their own efforts; this is called 'self efficacy'. This requires the provision of tasks that are just inside the patient's level of competence, so that they have to make some learning effort, but do succeed. Reducing the number of errors made by the patient ('errorless learning') is also essential, as people with schizophrenia find it hard to distinguish in their memory between responses that produced errors, and responses that were correct. Thus, if they make many errors they will not be able to carry out the task correctly at a later date. The studies that have been carried out so far have used paper and pencil tasks or computer games to teach information processing skills and are usually supervised by clinical psychologists, but Table 4.2 shows the sort of approaches that could be provided within any psychosocial treatment program.

Several meta-analyses, carried out on the data from controlled and randomized controlled trials^{34,35} demonstrate that the effect size of cognitive remediation or cognitive enhancement is about 0.5. However, it seems that these new psychosocial techniques are more likely to have an effect on functional outcome than medication enhancement. For example, Velligan et al³⁶ showed that cognition could be enhanced by quetiapine but that this had no effect on functioning, whereas Bell et al,¹⁶ Spaulding et al,³⁷ Wykes et al,^{29,38} Hogarty et al,³⁹ and McGurk et al⁴⁰ have shown that cognitive enhancement achieved through psychosocial means does lead to functional changes. More recent analyses to specifically test these effects have confirmed that random changes that are apparent in the control conditions of trials do not consistently lead to changes⁴¹.

The majority of studies on the rehabilitation of cognitive deficits approached the problem in a pragmatic way with little regard to the types of techniques that may be necessary or theories about the way in which cognitive deficits impinge on daily living. In the first book on individual cognitive enhancement, Wykes and Reeder³³ specifically approach the problem from this perspective and have drawn up a theory of implementation of executive and other cognitive functions in daily life. Their theory suggests the role of cognition in three simple pathways: routine actions, routine controlled actions, and non-routine actions. In the first type of action, behavior is

Table 4.2 Cognitive enhancement strategies for people with schizophrenia

<i>Life skill</i>	<i>Cognitive skills required</i>	<i>Useful strategies to aid relevant cognitive skills</i>	<i>Useful tasks to target relevant skills</i>
Shopping for groceries	Planning Memory Sequencing	Write a shopping list or repeat to yourself what you need to buy	Devising a plan for how to implement a problem-solving task
		Break the shopping list into categories	Re-ordering numbers from a disorganized list
		Order your list according to the layout of the shop(s)	Memorizing a set of words
		Check details frequently	
Reading a train timetable	Attention to detail Shifting attention Self-monitoring	Trace along lines with fingers to avoid visual neglect	Searching through a grid of letters for changing target letters
		Use verbal mediation to remind yourself what you are looking for	Line bisection tasks (estimating the midpoint of a line)
		Visualize the route	
		Generate a verbal description	Memorizing sequences of squares on a grid
Remembering the route to the shop	Spatial memory	Use verbal repetition	Memorizing designs
		Associate landmarks with familiar objects	Generating verbal descriptions for designs or sequenced patterns
		Make a list of landmarks	
		Draw yourself a map	
Planning your next move in a game of draughts	Spatial memory Planning Sequencing	Visualize the moves	
		Find visual patterns to describe the moves	Visual transformation tasks (e.g. draw what this shape would look like if it was rotated by half a turn)
		Generate a verbal description for the moves	Memorizing geometric patterns
		Use verbal repetition	Memorizing sequences of moves on a grid

Continued

Table 4.2 Cognitive enhancement strategies for people with schizophrenia

<i>Life skill</i>	<i>Cognitive skills required</i>	<i>Useful strategies to aid relevant cognitive skills</i>	<i>Useful tasks to target relevant skills</i>
Holding a conversation in a noisy room	Auditory verbal memory Comprehension Selective attention Self-monitoring	Minimize distractions Ask the other person to repeat what they said Don't rush what you are saying	Generating verbal descriptions for pictures Listening to instructions and then carrying them out Answering questions about a spoken passage Counting target items whilst tapping a sequence with your hand Comprehension tasks – learning a written passage and answering questions about it Searching for target letters or numbers in a grid Attentional shifting tasks: e.g. copying a design onto another sheet of paper Sequencing tasks – describe the steps needed to carry out problem-solving tasks
Reading a magazine article	Verbal comprehension Verbal memory Attention to detail	Use chunking Use repetition Follow each line with your finger to ensure nothing is missed out and reading speed is not too fast	
Baking a cake using a recipe	Sustained attention Shifting attention Sequencing Planning Memory Self-monitoring	Take one step at a time Organize your equipment Use written records Use verbal repetition Devise a plan before you begin Create subgoals Check steps as you proceed	

governed by a schema that requires no reflection and requires little cognitive control. Once the environmental trigger occurs, the behavior is automatic. These actions are unlikely to be affected by small changes in cognition functions. In the second type, routine controlled actions, the person has a cognitive schema to guide the action but may need to adapt it a little, e.g. to attend to specific parts of the schema. These actions can be improved in terms of their efficiency by improvement in cognitive functions but the effects are limited. Most of our actions require flexibility and these are the final category, non-routine controlled actions. For these actions we must develop new cognitive schema to guide us as to which are efficient. These actions require reflection on our own knowledge and Wykes and Reeder³³ have termed this 'metacognition'. It is their contention that teaching metacognition is essential if cognitive skills are to be translated into actions. Their book provides an overview of the techniques they think should be included to enhance the transfer of cognitive improvements into everyday life.

Changing rehabilitation programs to fit strengths

It seems obvious that cognitive difficulties need to be taken into account in providing any psychosocial rehabilitation program. This means obtaining a profile of the cognitive difficulties of a person and then using this to guide the design of an individualized program. For example, poor verbal memory is known to limit learning in a social skills training program. The most sensible response is to change the program itself so that it does not rely too heavily on verbal memory. This sort of approach has been adopted in the learning disability literature, but has not been investigated extensively in programs for people with schizophrenia.

Changing the environment

This is the last resort for the treatment of cognitive difficulties, and is similar to the approaches made for people with dementia or head injury. Here, the environment is changed so that there is less demand on the dysfunctional cognitive systems. One randomized trial in Texas showed that by providing this sort of support patients with cognitive difficulties improved their overall functioning⁴². The key worker/case manager visits the person at least twice a week and provides a series of cues for carrying out particular tasks, such as alarms to remind them when to go out to the day center. They also organize their activities minutely, e.g. placing all the clothes required for a single day into boxes and labeling them with the days of the week; the person then puts

all the clothes on for that particular day, no more and no less⁴². This form of therapy, known as ‘cognitive adaptational training’ could be seen as rather intrusive, and may not be acceptable to some services and patients.

Conclusions

Cognitive impairments are common in schizophrenia, and mediate much of the disability experienced by people with the condition. The atypical antipsychotics may be associated with some degree of improvement in cognition but it is the psychosocial forms of therapy that seem to offer the most benefit. These therapies are still under development but have shown effects on a wide range of everyday behaviors such as work and social function.

References

1. Harvey P, Serper M. The nature and management of cognitive dysfunction in patients with schizophrenia. *Dir Psychiatry* 1999; 19: 21–35.
2. Cannon M, Caspi A, Moffitt TE et al. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. *Arch Gen Psychiatry* 2002; 59: 449–56.
3. Lewis G, David AS, Malmberg A, Allebeck P. Non-psychotic psychiatric disorder and subsequent risk of schizophrenia: cohort study. *Br J Psychiatry* 2000; 177: 416–20.
4. Reichenberg A, Weiser M, Caspi A et al. Premorbid intellectual functioning and risk of schizophrenia and spectrum disorders. *J Clin Exp Neuropsychol* 2006; 28: 193–207.
5. Saykin AJ, Shtasel DL, Gur RE et al. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Arc Gen Psychiatry* 1994; 51: 124–31.
6. Jeste DV, Harris MJ, Krull A et al. Clinical and neuropsychological characteristics of patients with late-onset schizophrenia. *Am J Psychiatry* 1995; 152: 722–30.
7. Goldberg TE, Weinberger DR. Probing prefrontal function in schizophrenia with neuropsychological paradigms. *Schizophr Bull* 1988; 14: 179–83.
8. Albus M, Hubmann W, Ehrenberg C et al. Neuropsychological impairment in first-episode and chronic schizophrenic patients. *Eur Arch Psychiatr Clin Neurosci* 1996; 246: 249–55.
9. Greenwood K. The nature and stability of executive impairments in schizophrenia. PhD Thesis, University of London, 2000.
10. Cornblatt BA, Lenzenweger MF, Dworkin RH, Erlenmeyer-Kimling L. Positive and negative schizophrenic symptoms, attention, and information processing. *Schizophrenia Bulletin* 1985; 11: 397–408.
12. Johns LC, Rossell S, Frith C et al. Verbal self-monitoring and auditory verbal hallucinations in patients with schizophrenia. *Psychol Med* 2001; 31: 705–15.
13. Frith C. *The Cognitive Neurophysiology of Schizophrenia*. Hove, UK: Lawrence Erlbaum Associates, 1992.
14. Wykes T, Dunn G. Cognitive deficit and the prediction of rehabilitation success in a chronic psychiatric group. *Psychol Med* 1992; 22: 389–39.

15. Patel A, Everitt B, Knapp M et al. Schizophrenia patients with cognitive deficits: factors associated with costs. *Schizophr Bull* 2006; 32: 776–85.
16. Bell M, Bryson G, Tamasine G, et al. Neurocognitive enhancement therapy with work therapy: effects on neuropsychological test performance. *Arch Gen Psychiatry* 2001; 58: 763–8.
17. Gold J, Iannone V, McMahon R, Buchanon R. Cognitive correlates of competitive employment among patients with schizophrenia. *Schizophr Res* 2001; 49: 134.
18. Bellack A, Green M, Cook J et al. Assessment of Community Functioning in People With Schizophrenia and Other Severe Mental Illnesses: A White Paper Based on an NIMH-Sponsored Workshop. *Schizophr Bull* 2007; 33: 805–22.
19. Bowie C, Reichenberg A, Patterson TL et al. Determinants of real-world functional performance in schizophrenia subjects: correlations with cognition, functional capacity, and symptoms. *Am J Psychiatry* 2006; 163: 418–25.
20. Wykes T. Predicting symptomatic and behavioural outcomes of community care. *B J Psychiatry* 1994; 165: 486–92.
21. O'Carroll R. Cognitive impairment in schizophrenia. *Adv Psychiatr Treat* 2000; 6: 161–8.
22. Keefe RSE, Silva SG, Perkins DO, Lieberman JA. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. *Schizophr Bull* 1999; 25: 201–22.
23. Green MF, Marder SR, Glynn SM et al. The neurocognitive effects of low-dose haloperidol: a two-year comparison with risperidone. *Biol Psychiatry* 2002; 51: 972–8.
24. Keefe RS, Seidman LJ, Christensen BK et al. Long-term neurocognitive effects of olanzapine or low-dose haloperidol in first-episode psychosis. *Biol Psychiatry* 2006; 59: 97–107.
25. Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bul* 1999; 25: 233–55.
26. Bilder RM, Goldman RS, Volavka J et al. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. *Am J Psychiatry* 2002; 159: 1018–28.
27. Harvey PD, Keefe RSE. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am J Psychiatry* 2001; 158: 176–84.
28. Wykes T, Reeder C, Corner J et al. The effects of neurocognitive remediation on executive processing in patients with schizophrenia. *Schizophr Bull* 1999; 25: 291–308.
29. Wykes T, Reeder C, Williams C et al. Are the effects of cognitive remediation therapy (CRT) durable? Results from an exploratory trial. *Schizophr Res* 2003; 61: 163–74.
30. Goff DC, Freudenreich O, Evins AE. Augmentation strategies in the treatment of schizophrenia. *CNS Spectr* 2001; 6: 904–11.
31. Levin ED, Rezvani A. Nicotinic-antipsychotic drug interactions and cognitive function. *EXS* 2006; 98: 185–205.
32. Wykes T, Van Der Gaag. Is it time to develop a new cognitive therapy for psychosis—cognitive remediation therapy (CRT)? *Clin Psychol Rev* 2001; 21: 1227–56.
33. Wykes T, Reeder C. *Cognitive Remediation for Schizophrenia: Theory and Practice*. London: Routledge, 2006.
34. Krabbendam L, Aleman A. Cognitive rehabilitation in schizophrenia: a quantitative analysis of controlled studies. *Psychopharmacology* 2003; 169: 376–82.
35. Twamley EW, Jeste DV, Bellack AS. A review of cognitive training in schizophrenia. *Schizophr Bull* 2002; 29: 359–82.

36. Velligan DI, Prihoda TJ, Sui D et al. The effectiveness of quetiapine versus conventional antipsychotics in improving cognitive and functional outcomes in standard treatment settings. *J Clin Psychiatry* 2003; 64: 524–31.
37. Spaulding W, Reed D, Sullivan M, et al. Effects of cognitive treatment in psychiatric rehabilitation. *Schizophrenia Bull* 1999; 25: 657–67.
38. Wykes T, Reeder R, Landau S et al. Cognitive remediation therapy in schizophrenia: a randomised controlled trial. *Br J Psychiatry* 2007; 190: 421–7.
39. Hogarty GE, Flesher S, Ulrich R et al. Cognitive enhancement therapy for schizophrenia: effects of a 2-year randomized trial on cognition and behavior. *Arch Psychiatry* 2004; 61: 866–76.
40. McGurk SR, Mueser KT, Pascaris A. Cognitive training and supported employment for persons with severe mental illness: one year results from a randomized controlled trial. *Schizophr Bul* 2005; 31: 898–909.
41. Reeder C, Smedley N, Butt K et al. Cognitive predictors of social functioning improvements following cognitive remediation for schizophrenia. *Schizophr Bull* 2006; 32(Suppl 1): S123–31.
42. Velligan DI, Bow-Thomas CC, Huntzinger CD et al. A randomized controlled trial of the use of compensatory strategies in schizophrenic outpatients: cognitive adaptation training. *Am J Psychiatry* 2000; 157: 1317–23.

Depression and anxiety in schizophrenia

David J Castle, Til Wykes, and Natalie Knoesen

The extent of psychiatric comorbidity in schizophrenia is often not appreciated, in part because of our heritage of an essentially hierarchical approach to psychiatric diagnosis, where schizophrenia ‘trumps’ depression and anxiety. However, the recognition of depressive and anxiety symptoms in people with schizophrenia is important and has begun to receive increasing attention. These symptoms are common, tend to worsen the longitudinal course of illness, and can result in secondary morbidity and suicide. This chapter provides a brief overview of depression and selected anxiety disorders (social anxiety and obsessive-compulsive disorder (OCD)) in schizophrenia.

Depression and schizophrenia

The relationship between schizophrenia on the one hand, and affective disorders on the other, has dominated the nosological debate for well over a century since Kraepelin’s original dichotomization of ‘dementia praecox’ from ‘manic depression’¹. Bleuler, who coined the term ‘schizophrenia’, did include affective symptoms (anhedonia) in his definition of the disorder². But it was Kasanin, in describing patients with what he called ‘schizoaffective disorder’, who shifted the debate to a consideration of patients with an admixture of both ‘schizophrenic’ and ‘affective’ symptoms³; the place of such disorders in the nosology is still debated⁴. Here we do not consider schizoaffective disorders as such, nor do we address manic psychoses, concentrating instead on depression in people with schizophrenia. For reviews of the treatment of schizoaffective disorder, see Azorin^{5,6} and Levinson et al⁴.

It is not uncommon for people with schizophrenia to manifest depressive symptoms. Indeed, the National Comorbidity Survey in the US reported that

59% of people with schizophrenia also had a lifetime diagnosis of depression. In clinical samples of schizophrenia patients, rates of depression of anything from 7 to 65% have been reported, dependent upon sample selection and the definition of depression; Siris^{7,8}, who has reviewed these studies, suggests a modal figure of 25%.

The extent of this comorbidity is, in many ways, unsurprising, as many people with schizophrenia suffer from secondary social dysfunction, including the break-up of families and relationships, loss of study/work, and poverty (see Box 5.1). Such factors are associated in the general population with depression. Furthermore, schizophrenia is a severe and long-term illness which carries with it considerable stigma and which is thus difficult for the patient to adjust to.

Effect of depression on the longitudinal course of schizophrenia

Some early studies suggested that depression in schizophrenia might be a predictor of favorable outcome, but such studies were almost certainly confounded by the inclusion of people with 'schizoaffective' disorders, and it is now generally accepted that depression worsens the long-term course of schizophrenia and is associated with increased use of medications, early relapse, and increased hospital admissions^{9–11}. Some recent studies have found that patients with comorbid depressive symptoms who have greater insight into their mental illness, its social consequences, and treatment efficacy, experience poorer overall quality of life, specifically relating to physical and psychological health, social relationships, and their environment^{12–15}. Such patients appear to be more at risk of depressive symptoms at the beginning of treatment, and of developing postpsychotic depression^{16,17}.

Box 5.1 Factors that might mediate depression in schizophrenia.

Social factors (unemployment, lack of social network, etc.)

Psychosocial stressors (e.g. loss of role, family stress)

Adjustment to diagnosis

Alcohol and illicit substance use

Non-compliance with antipsychotic medication

Direct dysphoric effect of antipsychotic medication

Extrapyramidal side-effects of antipsychotic medication

Correlations between level of insight, distress, hopelessness, and suicidality have also been reported^{14,16,18}.

The rates of completed suicide are far higher in schizophrenia patients than the general population. Most recent estimates indicate that around 5% of schizophrenia patients will commit suicide, and this usually occurs near illness onset¹⁹. In a single year, 3800 schizophrenia sufferers in the US committed suicide²⁰. Given the strong correlation between depressive symptoms, notably hopelessness, and suicide in schizophrenia^{10,20,21}, depression is a major risk factor for suicide in patients with schizophrenia. It is thus imperative that clinicians recognize and treat depression in such individuals⁸.

Recognizing depression in schizophrenia

One of the impediments to the recognition of depression in people with schizophrenia is the diagnostic hierarchy alluded to above. Thus, clinicians tend to concentrate on eliciting and monitoring psychotic symptoms, rather than depression. The problem is made worse by the fact that both psychotic symptoms and side-effects of antipsychotic medication can manifest very much like depression, and the distinction can be difficult to make (see Box 5.2). For example, depressive lack of motivation and interest can be confused with the apathetic social withdrawal of schizophrenia, or might be considered a sign of ‘demoralization’²². Andreasen²³ suggests that the eliciting of vegetative symptoms such as anorexia or insomnia, or expressions of low self-esteem and guilt, should sway the diagnosis towards one of depression (see also Chapter 3).

Another factor to consider is that antipsychotic agents can produce side-effects that can mimic depression. Akinesia can be missed clinically as it does not always occur in the setting of obvious parkinsonism²⁴. Akathisia is also associated with mood symptoms, notably dysphoria, and has been linked with suicide²⁵. Such side-effects are important to recognize and treat, as outlined below.

Box 5.2 Psychotic symptoms and antipsychotic side-effects presenting as depression.

Positive psychotic symptoms
Negative symptoms
Akinesia
Akathisia

Do antipsychotics cause depression?

There is considerable debate about whether antipsychotics actually cause depression. Siris⁷ points to three sets of findings that suggest that use of antipsychotics is not a major factor:

- Depressive symptoms tend to improve as psychotic symptoms improve.
- Similar rates of depression have been reported in schizophrenia patients on and off antipsychotics.
- Studies have failed to show any consistent correlation between depressive symptoms and antipsychotic dose or plasma level.

However, other authors refute this conclusion, and have suggested a role for antipsychotic-mediated effects on dopamine-mediated reward systems in the brain as etiologically important²⁶.

Any dysphoric effect of antipsychotics is not likely to be prominent with the newer 'atypical' agents (see Chapter 1). Indeed, risperidone, olanzapine, and ziprasidone have all been shown to have antidepressant effects in schizophrenia patients^{27–31}. It is supposed that the antidepressant effect is dictated by the serotonergic actions of these drugs, although a number of other parameters should also be considered (see Box 5.3). In an important study that controlled for the effects of lower extrapyramidal side-effects (EPSE) with olanzapine compared with haloperidol, Tollefson et al³² employed path analysis to show a direct antidepressant effect of olanzapine. Similarly, Emsley et al's path analysis study³³ compared quetiapine with haloperidol and found a greater direct reduction in depressive symptoms, independent of positive, negative, or extrapyramidal symptoms, with quetiapine.

Box 5.3 Ways in which atypical antipsychotics may produce antidepressant effects.

Tend not to produce extrapyramidal side-effects at therapeutic doses
 Tend not to produce neuroleptic-induced deficit symptoms (NIDS)
 More efficacy against negative symptoms (notably clozapine)
 Reduce illicit substance use
 Enhance compliance with medication
 Enable more effective psychosocial rehabilitation, including work
 Direct antidepressant effect

Based on reference 31.

Box 5.4 Factors to exclude in schizophrenia patients presenting with depression.

Organic disorders (medical)
 Alcohol abuse
 Illicit substance use
 'Prepsychotic' prodromal phase of psychotic episode
 Negative symptoms (e.g. anergia, apathetic social withdrawal)
 Schizoaffective depression
 Antipsychotic side-effects (notably akinesia and akathisia)
 Demoralization (diminished sense of subjective control over the illness)

Adapted from references 7, 8, and 31.

A randomized controlled study by Kotler et al³⁴ found significant improvements in depressive symptomatology with sulpiride augmentation of olanzapine in treatment-resistant chronic schizophrenia patients.

Treating depression in schizophrenia

Box 5.4 presents some factors that should be excluded in schizophrenia patients presenting with depression. Some of these might require a therapeutic trial, for example, an anticholinergic challenge if akinesia is suspected, and propranolol or a benzodiazepine in patients with akathisia. It is also important to recognize that there is little evidence for the efficacy of antidepressant medication for dysphoria in patients who have prominent positive symptoms of psychosis, and the priority should be the optimal control of psychotic symptoms⁷.

Psychological strategies

The treatment of depression in schizophrenia requires a multifaceted biopsychosocial approach. Life events resulting from an acute episode and the stigma attached to the illness as well as the loss of social roles are known to be associated with depression in schizophrenia³⁵. Psychological factors associated with psychotic symptoms are also likely to predict depression. For instance, the degree of malevolence of the content of an auditory hallucination and the powerfulness of the 'voice' are predictive of depression.

Recent research suggests that greater insight into illness is associated with an increase in depression and poorer subjective quality of life in people with schizophrenia. However, insight into illness is crucial for better acceptance of

illness, adherence to treatment, and rehabilitation³⁶. This dichotomy has important implications for treatment and suggests an emphasis on psychoeducation programs focusing on depressive symptoms and quality of life-related aspects. Recent studies have found support for such psychoeducation programs and have reported significant improvements in quality of life, competence, control, and overall well-being^{37,38}. This, together with increased awareness of these issues by the clinician and a strengthening of the therapeutic alliance, may help improve insight without the risk of depressed mood and quality of life³⁶.

The overall psychological strategy for ameliorating depression in people with schizophrenia should be to encourage a blame-free acceptance and a mastery of the illness³⁵. A cognitive approach to symptoms and the appraisal of the self should therefore have an impact on depression. There is, however, little empirical evidence to support any specific psychological therapy in this context. Thus, interventions should be tailored to the particular needs of the individual within the overall model; for example, grief work should be provided for those experiencing loss, and rehabilitation and resocialization programs for those manifesting demoralization.

Pharmacological strategies

In terms of medication, it appears clear from the discussion above, that atypical antipsychotics will come to play an important role in the treatment of depression in schizophrenia. Siris³¹ reviewed 13 prospective randomized controlled trials of atypical antipsychotics in schizophrenia, and found that 12 of these recorded antidepressant efficacy. Similarly, Tollefson's review³⁹ of the role of antipsychotics in the treatment of comorbid mood disorders, reported more robust antidepressant treatment effects when using atypical antipsychotics. Many recent studies continue to find support for the antidepressant efficacy of atypical antipsychotics in schizophrenia^{28,33,34}. Thus, atypical antipsychotics seem a prudent choice in the setting of schizophrenia complicated by depression. A beneficial effect on suicidality would also be expected, and has been confirmed for clozapine⁴⁰.

The evidence regarding the efficacy of the addition of antidepressants to antipsychotics is rather mixed, and some studies have reported a worsening of psychotic symptoms with this combination. In reviewing this literature, Levinson et al⁴ found 'substantial evidence' for the efficacy of the addition of an antidepressant in schizophrenia patients who develop a full major depressive syndrome after resolution of psychosis. The evidence regarding depressive symptoms not meeting syndromic 'caseness' is equivocal, and in this setting

strategies such as optimization of antipsychotic treatment and psychosocial interventions should be considered prior to resorting to antidepressant medication. According to Buckley¹⁰, in acutely psychotic patients with comorbid depressive symptoms, it is best to first treat the psychosis with an atypical antipsychotic and see whether the depressive symptoms subside before adding an antidepressant or mood stabilizer. If antidepressants are added, their effect on mood requires close monitoring of overall symptomatology, and worsening of psychotic symptoms might require their withdrawal.

Dufresne⁴¹ has provided a useful overview of the potential problems arising from the addition of antidepressants to antipsychotic drugs in general. These include pharmacodynamic and pharmacokinetic effects that can exacerbate side-effects, such as the combination of two agents with anticholinergic or cardiotoxic effects. Common sense should prevail in choosing which combination of drugs to use, and side-effects monitored carefully, with drug levels being checked for combinations that affect each other's metabolism. In clinical practice, selective serotonin reuptake inhibitors (SSRIs) are often added to atypical antipsychotics in patients with persistent depression, and this combination is usually well tolerated. Preference should be given to those SSRIs that do not perturb the metabolism of the antipsychotic. The addition of lithium to an antipsychotic, and the place of electroconvulsive therapy (ECT) in depression in schizophrenia, have not been adequately studied, although they may be indicated in particular patients.

Whatever treatment is decided upon, it is best that clinicians 'partner with their patients' and be guided by the patient's clinical and functional outcome to develop an appropriate and effective treatment regimen^{42,43}.

Anxiety disorders in schizophrenia

It is often assumed that symptoms of anxiety in people with schizophrenia are secondary to positive psychotic symptoms (i.e. delusions and hallucinations). However, a number of studies have now confirmed substantial anxiety comorbidity in schizophrenia, not merely consequent upon positive symptoms. For example, Cassano et al⁴⁴ found, in their sample of 31 patients with schizophrenia spectrum disorders, that 58% were comorbid for another Diagnostic and Statistical Manual (DSM)-III-R psychiatric disorder, 19% had a lifetime diagnosis of panic disorder, 29% OCD, and 16% social phobia. In another study of patients with schizophrenia ($n = 60$), Cosoff and Hafner⁴⁵ found 12% were comorbid for generalized anxiety disorder, 13% for OCD,

and 17% for social phobia. Similarly, Goodwin et al⁴⁶ reported a rate of 15% for panic attacks in their sample of 120 people with psychotic disorders, while Bayle et al⁴⁷ found rates as high as 47.5% for a lifetime history of panic attacks ($n = 40$). Similar prevalence rates have been reported in more recent studies for comorbid OCD, panic disorder, and social anxiety disorder^{48–52}. In fact, a comprehensive review of the literature on anxiety comorbidity in schizophrenia conducted by Pokos and Castle⁵³ revealed an overall average rate of anxiety comorbidity of around 50% in clinical studies, significantly higher than in the general population. Braga et al's literature review⁵⁴ also reported high prevalence rates of anxiety comorbidity, particularly OCD, and panic disorder. Huppert and Smith's study⁵⁵ was one of the first to examine simultaneously the interaction of specific anxiety subtypes and psychosis, and found that obsessive-compulsive and social anxiety symptoms were related to increased positive symptoms (a finding also reported by Ongur and Goff⁵⁶), bizarre behavior, and decreased quality of life, while panic and social anxiety were related to suspiciousness/paranoia.

These high comorbidity rates are not found only in clinical samples. Indeed, Kendler et al⁵⁷ in the general population National Comorbidity Study in the US found that 26% of individuals with schizophrenia also met criteria for panic disorder. Table 5.1 provides a summary of the average prevalence rates of specific anxiety disorders in schizophrenia and related disorders compared with those found in the general population (reviewed by Pokos and Castle⁵³).

Studies investigating the temporal relationship between schizophrenia and comorbid anxiety disorders generally find that the anxiety disorders precede the onset of overt psychosis in at least 50% of patients⁵³. This is compatible with findings from the longitudinal Israeli High-Risk Study⁶⁰, where those who developed schizophrenia had higher anxiety ratings at the ages of 11 and 16 than those who did not. Similarly, Goodwin et al⁶¹ found that early neuroticism may be a precursor to the onset of psychotic symptoms, consistent with findings of Lewis et al⁶².

A fairly uniform finding is that anxiety comorbidity in schizophrenia is associated with a relatively worse illness outcome. For example, Goodwin et al⁶¹ found that psychosis patients with panic comorbidity did worse on outcomes such as psychiatric symptomatology, rehabilitation outcome, and quality of life, than their counterparts without panic. Similar findings were also reported by Cosoff and Hafner⁴⁵ for patients with comorbid generalized anxiety disorder. The negative impact of anxiety comorbidity in schizophrenia on quality of life has received increased recognition in recent years^{48,51,63–66}, with anxiety

Table 5.1 Rates of anxiety disorders in schizophrenia spectrum disorders (SSDs) compared with National Comorbidity Study⁵⁸ (NCS) and Epidemiological Catchment Area⁵⁹ (ECA) data (results from the most reliable studies given in brackets)

	<i>General population prevalence rates</i>	<i>Rates in SSDs</i>
NCS		
Total AD	25%	21–85% (~50%)
GAD	5%	1–31% (10–20%)
PD	3.5%	4–35% (4–20%)
AgP	5%	0–28% (5–20%)
SP	13%	1–40% (~30%)
SimP	11%	0–63% (5–15%)
ECA study		
OCD	2.5%	1–59% (11–15% or 22–30%*)

*Recent onset of SSDs vs. more chronic population, respectively.

Based on reference 53.

AD, anxiety disorders; GAD, generalized anxiety disorders; PD, panic disorders; AgP, agoraphobia; SP, social phobia; SimP, simple phobia; OCD, obsessive-compulsive disorder.

being regarded as more independently related to impaired quality of life than depression in patients with schizophrenia^{51,66}.

It is also the case that the anxiety comorbidity often goes unrecognized and hence not directly treated⁴⁵. It is important that all the experiences of schizophrenia patients are not dismissed as being part of their psychotic illness, as the mere acknowledgment of anxiety symptoms as 'non-psychotic' can be both reassuring and empowering for the patient.

Social anxiety disorder

Some degree of impairment of social functioning is not unusual in schizophrenia, particularly in the occupational, self-care, and independent living domains⁶⁷. Diminished social functioning might be secondary to positive symptoms, negative symptoms, or to the disruption of social maturation and adeptness that the early onset of a severe psychiatric disorder can bring. These problems are compounded by stigmatization and negative attitudes in the general population, regarding schizophrenia. A recent study conducted by Pallanti et al⁶⁸ showed a worse outcome for schizophrenia patients with comorbid social

phobia with respect to suicide attempts, substance abuse, social adjustment, and overall quality of life.

It is often assumed that social dysfunction in schizophrenia is part and parcel of the illness process, and that little can be done to ameliorate it. This is not the case. Indeed, social skills training has a track record in rehabilitation of schizophrenia, confirmed in a recent Spanish study conducted by Moriana et al⁶⁹. However, social skills training is not effective for all patients, and when gains accrue they often do not generalize to new situations⁷⁰. Furthermore, it is often the case that social anxiety disorder as such is not considered as a dependent variable in investigations of social skills training⁷¹. However, some studies are beginning to investigate social anxiety in schizophrenia patients directly. In fact, Pallanti et al⁶⁸ reported that social anxiety was the most prevalent anxiety disorder in schizophrenia patients, a finding also supported in an earlier study by Cosoff and Hafner⁴⁵.

In terms of treatment, Halperin et al⁷² piloted a group-based intervention specifically targeting social anxiety disorder in people with schizophrenia. An outline of the program is shown in Box 5.5. This study reported gains in terms of social anxiety, mood, and overall quality and enjoyment of life. Similarly, Kingsep et al⁷³ conducted a 12-week group cognitive behavioral therapy (CBT) program consisting of psychoeducation, graded exposure simulation,

Box 5.5 Outline of group-based program for social phobia in schizophrenia.

Session 1 Overview of anxiety, and social anxiety in particular; sharing of experiences/concerns by group members; setting objectives and first homework tasks (e.g., social exposure tasks, with monitoring and challenging of unhelpful automatic thoughts)

Session 2 Review of previous week, and of homework; introduction to cognitive restructuring, including challenging negative automatic thoughts

Session 3 Exposure exercise, with role play; review of cognitive restructuring

Session 4 Educational video on social phobia; further homework assignments

Sessions 5–7 Homework reviews, cognitive restructuring with increasing onus on participants to take initiative

Session 8 Social outing; closure and future individual planning

Adapted from reference 73.

Box 5.6 Suggestions for identifying obsessive-compulsive symptoms (OCD) in psychosis.

- Obsessions and compulsions are phenomenologically similar to those in pure OCD, as described in the DSM-IV
- A repetitious act in response to psychotic ideation, and not in response to an obsession, does not constitute a compulsion
- Recurrent, intrusive, ego-dystonic thoughts with current delusional themes should not be regarded as an obsession. A reassessment after acute psychotic symptoms have been treated may be necessary
- Thought form disorder may confound a diagnosis of obsessive-compulsive symptoms (OCS). Treat the thought form disorder first and then reassess for OCS
- Primary obsessional slowness may be mistaken for prodromal schizophrenia or thought disorder as such patients may be unable to articulate obsessions and exhibit no compulsions
- In cases where it is difficult to determine real OCS in psychosis, empiric treatment with a neuroleptic and a serotonin reuptake inhibitor may be necessary

Based on reference 80.

cognitive restructuring, and role playing, and reported significant improvements in social anxiety, general psychopathology, depression, and quality of life. Important further steps will be to determine precisely which elements of this sort of intervention (in Box 5.5) are effective, and to integrate those elements into social skills training packages.

Harvey et al⁶⁷ investigated the benefits of a pharmacological approach to enhancing social competence in patients with schizophrenia. Short-term treatment with the atypical antipsychotics quetiapine and risperidone was associated with short-term improvements in social competence and positive correlations with cognitive ability. However, atypical antipsychotics may accentuate the risk of disorders like social phobia, necessitating careful consideration and monitoring especially with compounds such as clozapine or olanzapine⁶⁸. Given the lack of operational guidelines for the treatment of comorbid social anxiety disorder in schizophrenia, further research is needed to determine appropriate next-step treatments, be it psychological, pharmacological, or a combination of the two.

Obsessive-compulsive disorder

The co-occurrence of obsessive-compulsive symptoms (OCS) or full-blown OCD and schizophrenia has been recognized for decades, but, until more recently, has been the principal subject of few investigations⁷⁴. Indeed, Fabisch et al⁷⁵ could find only nine studies between 1926 and 2001 that directly investigated the prevalence of OCS in schizophrenia. More recently, comorbid OCD has received increased attention with a number of studies investigating the co-occurrence of OCD in schizophrenia^{49,55,56,76–78}. Reported rates vary widely (anything from 1% to 59%), depending on sample selection and diagnostic criteria employed. Identifying OCS in patients with schizophrenia can often be a rather difficult task exacerbated by the lack of a universally accepted technique for diagnosing symptom co-expression (see Box 5.6 for diagnostic suggestions). In one of the most methodologically sound of these studies, Eisen et al⁸⁰ found that six (7.7%) of 77 patients with schizophrenia or schizoaffective disorder also met DSM-III-R criteria for OCD; this rate is two to three times that reported in general population samples. The majority of studies found that OCS tended to antedate psychotic ones^{81–85}.

The reasons for the co-aggregation of OCS and psychotic symptoms have not been established. Stengel⁸⁶ and Rosen⁸⁷ believed that the occurrence of such features were to some degree protective against ‘personality disintegration’ in schizophrenia, but more recent studies suggest that schizophrenia patients with OCS actually have a worse longitudinal outcome and greater impairment in neuropsychological functioning (especially prefrontal dysfunction) than their counterparts without such symptoms. For example, in the Chestnut Lodge 16-year follow-up of chronic schizophrenia patients, those with OCS had a particularly poor outcome in terms of psychopathology, social and occupational functioning, and global outcome⁸⁸. A number of later studies have confirmed higher rates of social impairment^{89–92} and poorer functioning^{80,93–96} in comorbid OCS patients. Lysaker et al⁷⁷ reported greater levels of hopelessness in schizophrenia patients with significant levels of comorbid OCS compared with those without such symptoms.

Fenton and McGlashan⁸⁸ offer the following possible explanatory hypotheses for the coaggregation of OC and psychotic symptoms:

- There is a specific subtype of schizophrenia with OCS, and which has a pernicious course.
- These patients have two comorbid disorders, which additively contribute to a poor prognosis.
- Early onset of OCD impairs the individual’s social development and thus contributes to social disability when schizophrenia manifests.

A more recent study conducted by Bottas et al⁷⁹ found epidemiological and neurobiological evidence for a specific pattern of neurobiological dysfunction in patients with comorbid OCD and schizophrenia, supporting the notion of a schizo-obsessive subtype of schizophrenia (hypothesis 1 of Fenton and McGlashan⁸⁸). The results of their review emphasized that clinicians should distinguish between OCS that occur only in the context of psychosis and that may overlap with psychotic phenomenology, representing a forme fruste of psychosis; OCS occurring only in the prodromal phase of schizophrenia; neuroleptic-induced OCS or OCD; and OCS or OCD occurring concurrently with schizophrenia⁷⁹.

Treatment of obsessive-compulsive disorder in schizophrenia

The treatment of OCS or OCD in schizophrenia has not been adequately studied, resulting in no standard treatment regimen. However, there are some suggested therapeutic approaches to assist in the management of this difficult-to-treat patient subgroup. In terms of psychological techniques, behavioral therapy for OCS in schizophrenia can be employed effectively in some such patients, and may obviate the need for polypharmacy. A case study looking at the benefits of exposure and response prevention (ERP) (where OCS were separate from the psychotic experience) reported a marked reduction in the severity, distress, and impact of long-term OCS without leading to significant deterioration of psychotic symptoms⁹⁷. However, ERP relies on adequate perception and sustained attention, encoding and recall, and executive processing, and thus neuropsychological impairment in any of these information processing mechanisms (as often demonstrated in patients with schizophrenia and comorbid OCD) may lead to poorer outcomes with ERP treatment.

The benefits of CBT have been reported in many recent studies and have shown improvements in anxiety-related symptoms in psychosis^{98,99}. McKay and McKiernan¹⁰⁰ recommend the following stepwise procedure when using CBT to treat schizophrenia with comorbid OCD:

- first treat the positive symptoms with an appropriate antipsychotic;
- assess overvalued ideas;
- ERP with shorter exposure sessions;
- cognitive therapy, focusing specifically on the process of habituation and adaptive coping strategies;
- cognitive rehabilitation, focusing on memory, organization, and social skills to enhance the information processing mechanisms.

The pharmacological treatment of OCS in the setting of schizophrenia is mostly guided by the extant OCD literature. Thus, clinicians tend to rely on the compelling evidence for the efficacy of treatment with serotonergic antidepressants (clomipramine, SSRIs) in uncomplicated OCD^{101–103} and employ these in comorbid cases in addition to antipsychotic therapy^{104,105}. However, clomipramine's anticholinergic properties, and cardiovascular and weight gain side-effects may limit its use with some patients (e.g. those on clozapine), making SSRIs the favored choice in most cases.

A curious issue which has arisen with the advent of the atypical antipsychotics, notably clozapine (see Chapter 1) is the tendency of such agents to exacerbate, or produce *de novo*, OCS^{56,101,106–108}. The putative mechanism implicates the serotonin-5HT actions of these agents, though this has not been rigorously tested. In contrast, Poyurovsky et al¹⁰⁹ reported a positive therapeutic effect of olanzapine monotherapy in three schizo-obsessive patients who had otherwise been unresponsive to conventional antipsychotics in combination with anti-obsessive agents. Reznik et al¹¹⁰ hypothesized that OCS occurring within the course of psychosis may be effectively treated with clozapine alone, whilst OCS preceding psychosis may worsen with clozapine monotherapy and should rather be treated concomitantly with specific anti-obsessive agents. On the other hand, some antipsychotic medications, particularly those with sedative properties, can diminish anxiety⁵³.

A recent case study reported by Chaves et al¹¹¹ found support for the benefits of ECT in treating this comorbidity. Marked reductions in aggressive, psychotic, and OCS were observed, indicating that ECT may be an appropriate treatment in some cases, although typically regarded as a last resort. Poyurovsky et al¹⁰⁹ recommend a seven-step treatment algorithm, which is guided by patient response/lack of response, beginning with (1) atypical antipsychotic monotherapy, (2) then adding a SSRI, (3) switching to an alternative SSRI, (4) trying a typical antipsychotic and SSRI combination, (5) a low dose of clozapine monotherapy, (6) a clozapine/SSRI combination, and as a last resort (7) ECT.

The treatments outlined above (i.e. serotonergic antidepressants, behavioral therapy) can be effectively employed in this clinical scenario, and discontinuation of the atypical antipsychotic is not usually necessary^{74,112,113}. However, when combining antipsychotic and anti-OC medications, it is important to be mindful of possible pharmacological interactions and thus careful monitoring of blood levels and side-effects is necessary.

Conclusions

Depression and anxiety are common in patients with schizophrenia, and are often associated with a worsening of the long-term illness outcome. Despite this clear link, the nosological implications remain unclear, necessitating more etiologically orientated classification systems. Clinically, better recognition and adequate treatment of symptoms of depression and anxiety are required.

References

1. Kraepelin E. *Psychiatrie* (4th Edition). 1896: Leipzig: JA Barth.
2. Bleuler E. *Dementia praecox or the group of schizophrénias*. 1911, New York: International Universities Press.
3. Kasanin J. The acute schizoaffective psychoses. *Am J Psychiatry* 1933; 13: 97–126.
4. Levinson DF, Umapathy C, Musthaq M. Treatment of schizoaffective disorders and schizophrenia with mood symptoms. *Am J Psychiatry* 1999; 156: 1138–1148.
5. Azorin JM. Phenomenologic complexity of mania. *Encephale* 2001; 27: 485–7.
6. Azorin JM, Kaladjian A, Fakra E. Current issues on schizo-affective disorder. *Encephale* 2005; 31: 359–65.
7. Siris SG. Diagnosis of secondary depression in schizophrenia: implications for DSM-IV. *Schizophr Bull* 1991; 17: 75–98.
8. Siris SG. Managing depression in schizophrenia. *Psychiatric Annals* 2005; 35: 60–9.
9. Addington DD, Azorin JM, Falloon IRH et al. Clinical issues related to depression in schizophrenia: an international survey of psychiatrists. *Acta Psychiatr Scand* 2002; 105: 189–95.
10. Buckley PF. Affective impairment in schizophrenia: depression/anxiety. *Prim Psychiatry* 2005; 12: 4–6.
11. Siris SG. Schizophrenia. In: SR Hirsch, DR Weinberger (eds.) *Schizophrenia*. Oxford: Blackwell science, UK 1995.
12. Drake RJ, Pickles A, Bentall RP et al. The evolution of insight, paranoia and depression during early schizophrenia. *Psychol Med* 2004; 34: 285–92.
13. Mintz AR, Addington J, Addington D. Insight in early psychosis: a 1-year follow-up. *Schizophr Res* 2004; 67(2–3): 213–17.
14. Schwartz RC, Smith SD. Suicidality and psychosis: the predictive potential of symptomatology and insight into illness. *J Psychiatr Res* 2004; 38: 185–91.
15. Sim K, Mahendran R, Siris SG, Heckers S, Chong SA. Subjective quality of life in first episode schizophrenia spectrum disorders with comorbid depression. *Psychiatr Res* 2004; 129: 141–7.
16. Carroll A, Fattah S, Clyde Z et al. Correlates of insight and insight change in schizophrenia. *Schizophr Res* 1999; 35: 247–53.
17. Iqbal Z, Birchwood M, Chadwick P, Trower P. Cognitive approach to depression and suicidal thinking in psychosis 2. Testing the validity of a social ranking model. *Br J Psychiatry* 2000; 177: 522–8.
18. Kim Y, Sakamoto K, Kamo T, Sakamura Y, Miyaoka H. Insight and clinical correlates in schizophrenia. *Compr Psychiatry* 1997; 38: 117–23.
19. Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a re-examination. *Arch Gen Psychiatry* 2005; 62: 247–53.

20. Jones JS, Stein DJ, Stanley B et al. Negative and depressive symptoms in suicidal schizophrenics. *Acta Psychiatrica Scand* 1994; 89: 81–7.
21. Siris SG. Suicide and schizophrenia. *J Psychopharmacol* 2001; 15: 127–35.
22. Frank JD. *Persuasion and healing*. 1973; Baltimore: John Hopkins University Press.
23. Andreasen NC. Mood disorders and schizophrenia. *J Clin Psychiatry* 1998; 16: 7–8.
24. Van Putten T, May PRA. 'Akinetic depression' in schizophrenia. *Arch Gen Psychiatry* 1978; 35: 1101–7.
25. Drake RE, Ehrlich J. Suicide attempts associated with akathisia. *Am J Psychiatry* 1985; 142: 499–501.
26. Harrow M, Yonan C, Sands JR, Marengo J. Depression in schizophrenia: are neuroleptics, akinesia, or anhedonia involved? *Schizophr Bull* 1994; 20: 327–38.
27. Breier A, Berg PH, Thakore JH et al. Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia. *Am J Psychiatry* 2005; 162: 1879–87.
28. Kinon BJ, Lipkovich I, Edwards SB et al. A 24-week randomized study of olanzapine versus ziprasidone in the treatment of schizophrenia or schizoaffective disorder in patients with prominent depressive symptoms. *J Clin Psychopharmacol* 2006; 26: 157–62.
29. Lieberman JA, Stroup TS, McEvoy JP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; 353(12): 1209–23.
30. Simpson GM, Glick ID, Weiden PJ, Romano SJ, Siu CO. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Am J Psychiatry* 2004; 161: 1837–47.
31. Siris SG. Depression in schizophrenia: prespective in the era of 'atypical' antipsychotic agents. *Am J Psychiatry* 2000; 157: 1379–89.
32. Tollefson GD, Sanger TM, Lu Y, Thieme ME. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. *Arch Gen Psychiatry* 1998; 55: 250–8.
33. Emsley RA, Buckley P, Jones AM, Greenwood MR. Differential effect of quetiapine on depressive symptoms in patients with partially responsive schizophrenia. *J Psychopharmacol* 2003; 17: 210–15.
34. Kotler M, Strous RD, Reznik I, Schwartz S, Weizman A, Spivak B. Sulpiride augmentation of olanzapine in the management of treatment-resistant chronic schizophrenia: evidence for improvement of mood symptomatology. *Int Clinical Psychopharmacol* 2004; 19: 23–26.
35. Birchwood M, Iqbal I. Depression and suicidal thinking in psychosis. In: Wykes T, Tarrier N, Lewis S, eds. *Innovation and Outcome in Psychological Treatment of Schizophrenia*. Chichester: Wiley, 1998; 81–118.
36. Karow A, Pajonk FG. Insight and quality of life in schizophrenia: recent findings and treatment implications. *Curr Opin Psychiatry* 2006; 19: 637–41.
37. Pekkala E, Merinder L. Psychoeducation for schizophrenia. *Cochrane Database Syst Rev* 2002; (2): CD002831.
38. Sibitz I, Gossler R, Katschnig H, Amering M. 'Knowing-enjoying-better living'. A seminar for persons with psychosis to improve their quality of life and reduce their vulnerability. *Psychiatr Prax* 2006; 33: 170–6.
39. Tollefson GD. Role of the novel antipsychotics in the treatment of comorbid mood disorders in schizophrenia. In: A Breier, PV Tran, JM Herrera, GD Tollefson, FP Bymaster (eds.). *Current issues in the psychopharmacology of schizophrenia*. Philadelphia, PA: Lippincott Williams & Wilkins Publishers, 2001; pp. 497–512.
40. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic resistant schizophrenia: Impact on risk-benefit assessment. *Am J Psychiatry* 1995; 152: 183–90.

41. Dufresne RL. Issues in pharmacotherapy: focus on depression in schizophrenia. *Psychopharmacol Bull* 1995; 31: 789–96.
42. Ginsberg DL, Schooler NR, Buckley PF, Harvey PD, Weiden PJ. Optimizing treatment of schizophrenia. Enhancing affective/cognitive and depressive functioning. *CNS Spectrums* 2005; 10: 1–13.
43. Siris SG. Treating depression in schizophrenia (reply to Lund et al.). *Am J Psychiatry* 2001; 158: 1528.
44. Cassano GB, Pini S, Saettoni M, Rucci P, Dell'Osso L. Occurrence and clinical correlates psychiatric comorbidity in patients with psychotic disorders. *J Clin Psychiatry* 1998; 59: 60–8.
45. Cosoff SJ, Hafner J. The prevalence of comorbid anxiety in schizophrenia, schizoaffective disorder and bipolar disorder. *Aus NZ J Psychiatry* 1998; 32: 67–72.
46. Goodwin R, Stayner DA, Chinman MJ, Davidson L. Impact of panic attacks on rehabilitation and quality of life among persons with severe psychotic disorders. *Psychiatr Serv* 2001; 52: 920–4.
47. Bayle FJ, Krebs MO, Epelbaum C, Lery D, Hardy P. Clinical features of panic attacks in schizophrenia. *Eur Psychiatry* 2001; 26: 349–53.
48. Braga RJ, Mendlowicz MV, Marrocos RP, Figueira IL. Anxiety disorders in outpatients with schizophrenia: prevalence and impact on the subjective quality of life. *J Psychiatr Res* 2005; 39: 409–14.
49. Byerly M, Goodman W, Acholonu W, Bugno R, Rush AJ. Obsessive compulsive symptoms in schizophrenia: frequency and clinical features. *Schizophr Res* 2005; 76: 309–16.
50. Craig T, Hwang MY, Bromet EJ. Obsessive-compulsive and panic symptoms in patients with first-admission psychosis. *Am J Psychiatry* 2002; 159: 592–8.
51. Huppert JD, Smith TE. Longitudinal analysis of the contribution of anxiety and depression to quality of life in schizophrenia. *J Nerv Men Dis* 2001; 189: 669–75.
52. Muller JE, Koen L, Soraya S, Emsley RA, Stein DJ. Anxiety disorders and schizophrenia. *Curr Psychiatry Rep* 2004; 6: 255–61.
53. Pokos V, Castle DJ. Prevalence of comorbid anxiety disorders in schizophrenia spectrum disorders: a literature review. *Curr Psychiatry Rev* 2006; 2: 285–307.
54. Braga RJ, Petrides G, Figueira I. Anxiety disorders in schizophrenia. *Compr Psychiatry* 2004; 45: 460–468.
55. Huppert JD, Smith TE. Anxiety and schizophrenia: the interaction of subtypes of anxiety and psychotic symptoms. *CNS Spectr* 2005; 10: 721–31.
56. Ongur D, Goff DC. Obsessive-compulsive symptoms in schizophrenia: Associated clinical features, cognitive function and medication status. *Schizophr Res* 2005; 75: 349–62.
57. Kendler KS, Gallagher TJ, Abelson JM, Kessler RC. Lifetime prevalence, demographic risk factors and diagnostic validity of non-affective psychosis as assessed in a US community sample. *Arch Gen Psychiatry* 1996; 53: 1022–31.
58. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994; 51: 8–19.
59. Robins LN, Locke BZ, Regier DA. Overview: Psychiatric disorders in America. In: LN Robins, DA Regier (eds). *Psychiatric disorders in America*. 1991, New York: Free Press: 328–66.
60. Kugelmass S, Faber N, Ingraham LJ et al. Reanalysis of SCOR and anxiety measures in the Israeli High-Risk Study. *Schizophr Bull* 1995; 21: 205–17.
61. Goodwin RD, Ferrgusson DM, Horwood LJ. Neuroticism in adolescence and psychotic symptoms in adulthood. *Psychol Med* 2003; 33: 1089–97.
62. Lewis G, David AS, Malmberg A, Allebeck P. Non-psychotic psychiatric disorder and the subsequent risk of schizophrenia: cohort study. *Br J Psychiatry* 2000; 177: 416–20.

63. Hofer A, Kemmler G, Eder U et al. Quality of life in schizophrenia: the impact of psychopathology, attitude toward medication, and side effects. *J Clin Psychiatry* 2004; 65: 932–8.
64. Huppert JD, Weiss KA, Lim R, Pratt S, Smith TE. Quality of life in schizophrenia: contributions of anxiety and depression. *Schizophr Res* 2001; 51: 171–80.
65. Lysaker PH, Whitney KA, Davis LW. Clinical and psychosocial correlates of anxiety related symptoms in schizophrenia. In: Velonis CM (ed). *Anxiety Disorder Research*. Hauppauge, NY: Nova Science Publishers, 2005; pp. 1–19.
66. Wetherell JL, Palmer BW, Thorp SR et al. Anxiety symptoms and quality of life in middle-aged and older outpatients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry* 2003; 64: 1476–82.
67. Harvey PD, Patterson TL, Potter LS, Zhong K, Brecher M. Improvement in social competence with short-term atypical antipsychotic treatment: a randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition and neuropsychological functioning. *Am J Psychiatry* 2006; 163: 1918–25.
68. Pallanti S, Quercioli L, Hollander E. Social anxiety in outpatients with schizophrenia: a relevant cause of disability. *Am J Psychiatry* 2004; 161: 53–8.
69. Moriana JA, Alarcon E, Herruzo J. In-home psychosocial skills training for patients with schizophrenia. *Psychiatr Servi* 2006; 57(2): 260–2.
70. Wallace CJ, Nelson CJ, Lieberman RP, et al. A review and critique of social skills training with schizophrenia patients. *Schizophrenia Bull* 1980; 6: 42–63.
71. Penn DL, Hope DA, Spaulding W, Kucera J. Social anxiety in schizophrenia. *Schizophr Res* 1994; 11: 277–84.
72. Halperin S, Nathan P, Drummond P, Castle D. A cognitive-behavioural group-based treatment for social anxiety in schizophrenia. *Aust N Z J Psychiatry* 2000; 34: 809–13.
73. Kingsep P, Nathan P, Castle DJ. Cognitive behavioural group treatment for social anxiety in schizophrenia. *Schizophr Res* 2003; 63: 121–9.
74. Dowling FG, Pato MT, Pato CN. Comorbidity of obsessive-compulsive and psychotic symptoms: a review. *Harv Rev Psychiatry* 1995; 3: 75–83.
75. Fabisch K, Fabisch H, Langs G, Huber HP, Zapotoczky HG. Incidence of obsessive-compulsive phenomena in the course of acute schizophrenia and schizoaffective disorder. *Eur Psychiatry* 2001; 16: 336–41.
76. Kayahan B, Ozturk O, Veznedaroglu B, Eraslan D. Obsessive-compulsive symptoms in schizophrenia: prevalence and clinical correlates. *J Psychiatry Clin Neurosci* 2005; 59: 291–5.
77. Lysaker PH, Whitney KA, Davis LW. Obsessive-compulsive and negative symptoms in schizophrenia: associations with coping preference and hope. *Psychiatr Res* 2006; 141: 253–9.
78. Ongur D. About 30% of men with schizophrenia or schizoaffective disorders have obsessive-compulsive symptoms. *Evid Based Ment Health* 2006; 9–28.
79. Bottas A, Cooke RG, Richter MA. Comorbidity and pathophysiology of obsessive-compulsive disorder in schizophrenia: Is there evidence for a schizo-obsessive subtype of schizophrenia? *Psychiatry Neurosci* 2005; 30: 187–93.
80. Eisen JL, Beer DA, Pato MT, Venditto TA, Rasmussen STA. Obsessive compulsive disorder in patients with schizophrenia or schizoaffective disorder. *Am J Psychiatry* 1997; 154: 271–3.
81. Tibbo P, Kroetsch M, Chue P, Warneke L. Obsessive-compulsive disorder in schizophrenia. *J Psychiat Res* 2000; 34: 139–46.
82. Krüger S, Bräunig P, Höffler J, Shugar G, Börner I, Langkrär J. Prevalence of obsessive-compulsive disorder in schizophrenia and significance of motor symptoms. *J Neuropsychiatr Clin Neurosci* 2000; 12: 16–24.
83. Okasha A, Lotaief F, Ashour AM et al. The prevalence of obsessive compulsive symptoms in a sample of Egyptian psychiatric patients. *Encephale* 2000; 26: 1–10.

84. Ohta M, Kokai M, Morita Y. Features of obsessive-compulsive disorder in patients primarily diagnosed with schizophrenia. *Psychiatr Clin Neurosci* 2003; 57: 67–74.
85. Poyurovsky M, Kriss V, Weisman G et al. Comparison of clinical characteristics and comorbidity in schizophrenia patients with and without obsessive-compulsive disorder: schizophrenic and OC symptoms in schizophrenia. *J Clin Psychiatry* 2003; 64: 1300–7.
86. Stengel E. A study of some clinical aspects of the relationship between obsessional neurosis and psychotic reaction types. *J Mental Sci* 1945; 91: 166–87.
87. Rosen I. The clinical significance of obsessions in schizophrenia. *J Ment Sci* 1957; 103: 778–85.
88. Fenton WS, McGlashan TH. The prognostic significance of obsessive-compulsive symptoms in schizophrenia. *Am J Psychiatry* 1986; 143: 437–41.
89. Berman I, Kalinowski A, Berman SM, Lengua J, Green AI. Obsessive and compulsive symptoms in chronic schizophrenia. *Compr Psychiatry* 1995; 36: 6–10.
90. Dominguez RA, Backman KE, Lugo SC. Demographics, prevalence and clinical features of the schizo-obsessive subtype of schizophrenia. *CNS Spectrums* 1999; 4: 50–6.
91. Poyurovsky M, Hramenkov S, Isakov V et al. Obsessive-compulsive disorder in hospitalized patients with chronic schizophrenia. *Psychiatr Res* 2001; 102: 49–57.
92. Özdemir Ö, Tükel R, Turksoy N, Ücok A. Clinical characteristics in obsessive-compulsive disorder with schizophrenia. *Compr Psychiatry* 2003; 44: 311–16.
93. Hwang MY, Morgan JE, Losconzcy MF. Clinical and neuropsychological profiles of obsessive-compulsive schizophrenia: a pilot study. *J Neuropsychiatr Clin Neurosci* 2000; 12: 91–4.
94. Lysaker PH, Marks KA, Picone JB et al. Obsessive and compulsive symptoms in schizophrenia: clinical and neurocognitive correlates. *J Nerv Men Dis* 2000; 188: 78–83.
95. Lysaker PH, Bryson GJ, Marks KA, Greig TC, Bell MD. Association of obsessions and compulsions in schizophrenia with neurocognition and negative symptoms. *J Neuropsychiatr Clin Neurosci* 2002; 14: 449–53.
96. Nechmad A, Ratzoni GM, Poyurovsky M et al. Obsessive-compulsive disorder in adolescent schizophrenia patients. *Am J Psychiatry* 2003; 160: 1002–4.
97. Ekers D, Carman S, Schlich T. Successful outcome of exposure and response prevention in the treatment of obsessive compulsive disorder in a patient with schizophrenia. *Behav Cogn Psychotherapy* 2004; 32: 375–8.
98. Naem F, Kingdon D, Turkington D. Cognitive behaviour therapy for schizophrenia: relationship between anxiety symptoms and therapy. *Psychol Psychother* 2006; 79: 153–64.
99. Tarrier N. Co-morbidity and associated clinical problems in schizophrenia: Their nature and implications for comprehensive cognitive-behavioural treatment. *Behav Change* 2005; 22: 125–42.
100. McKay D, McKiernan K. Information processing and cognitive behaviour therapy for obsessive-compulsive disorder: comorbidity of delusions, overvalued ideas, and schizophrenia – A response paper. *Cogn Behav Pract* 2005; 12: 390–4.
101. Hood S, Alderton D, Castle DJ. Obsessive-compulsive disorder: treatment and treatment resistance. *Aust Psychiatry* 2001; 9: 118–27.
102. Hwang MY, Yum SY, Kwon JS, Opler LA. Management of schizophrenia with obsessive-compulsive disorder. *Psychiatr Ann* 2005; 35: 36–43.
103. Reznik I, Sirota P. An open study of fluvoxamine augmentation of neuroleptics in schizophrenia with obsessive and compulsive symptoms. *Clin Neuropharmacol* 2000; 23: 157–60.
104. Goff DC, Brotman AW, Waiters M, McCormick S. Trial of fluoxetine added to neuroleptics for treatment resistant schizophrenia. *Am J Psychiatry* 1990; 147: 492–4.

105. Zohar J, Kaplan Z, Benjamin J. Clomipramine treatment of obsessive-compulsive symptomatology in schizophrenic patients. *J Clin Psychiatry* 1993; 54: 385–8.
106. Lykouras L, Alevizos B, Michalopoulou P, Rabavilas A. Obsessive-compulsive symptoms induced by atypical antipsychotics. A review of the reported cases. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; 27: 333–46.
107. De Haan L, Oekeneva A, van Amelsvoort T, Linszen D. Obsessive-compulsive disorder and treatment with clozapine in 200 patients with recent-onset schizophrenia or related disorders. *Eur Psychiatry* 2004; 19: 524.
108. Ertugrul A, Yagcioglu A, Elif A, Eni N, Yazici KM. Obsessive-compulsive symptoms in clozapine-treated schizophrenic patients. *Psychiatr Clin Neurosci* 2005; 59: 219–22.
109. Poyurovsky M, Weizman A, Weizman R. Obsessive-compulsive disorder in schizophrenia: clinical characteristics and treatment. *CNS Drugs* 2004; 18: 989–1010.
110. Reznik I, Yavin I, Stryker R et al. Clozapine in the treatment of obsessive-compulsive symptoms in schizophrenia patients: a case series study. *Pharmacopsychiatry* 2004; 37: 52–6.
111. Chaves MPR, Crippa JAS, Morais SL, Zuardi AW. Electroconvulsive therapy for coexistent schizophrenia and obsessive-compulsive disorder. *J Clin Psychiatry* 2005; 66: 542–3.
112. Morrison D, Clark D, Goldfarb E et al. Worsening of obsessive-compulsive symptoms following treatment with olanzapine (letter). *Am J Psychiatry* 1998; 155: 855.
113. Randhawa RS. A review of the pharmacotherapy of obsessive-compulsive disorder and schizophrenia: The case of Sam. *Cog Behav Pract* 2005; 12: 395–402.

General health of people with schizophrenia

Urban Ösby, Peter Fahnstock, and John W Newcomer

Consistent evidence spanning different countries and practice settings indicates that individuals with schizophrenia have a shortened life expectancy, are at higher risk for development of medical conditions that negatively impact their health, are less likely to receive and benefit from medical treatment, are more likely to experience unfavorable clinical outcomes, and are more likely to die prematurely¹⁻⁷. These observations have led investigators to focus on risk factors that contribute to morbidity and mortality in patients with schizophrenia, and to more precisely characterize the incidence of natural and unnatural causes of death.

The average lifespan for individuals with schizophrenia is from 10 to more than 30 years shorter than that of the general population^{8,9}. Standardized mortality ratios (SMRs: a ratio of observed to expected deaths within a given age range) are a useful way to quantify the additional mortality risk associated with schizophrenia. The 'expected' mortality rate is the rate seen in the general population, whereas the 'observed' mortality rate is that seen in the population in question (e.g. schizophrenia patients). SMRs are particularly useful for identifying factors that contribute to the relative risk for different causes of death for psychiatric patients in comparison to the general population. They are less useful, however, for identifying factors that contribute to the absolute risk of death, and can therefore be potentially misleading. For example, as discussed below, cardiovascular disease is responsible for the largest number of absolute deaths in patients with schizophrenia⁶. However, since rates of death from cardiovascular disease are high in the general population as well, the SMR for cardiovascular disease is lower than the SMR for suicide, which is responsible for a lower number of absolute deaths of schizophrenia patients, but is relatively rare in the general population.

Medical causes of excess mortality in schizophrenia

Although SMRs for death by suicide are particularly high among individuals with schizophrenia, comorbid medical conditions actually confer the largest share of excess mortality in this population. Brown et al¹⁰, in a study of 370 patients with schizophrenia over 13 years, confirmed that more patients died from natural causes than unnatural causes: 73% died as a result of medical diseases. All-cause mortality SMR was 2.98 in the overall study population; disease-specific SMRs are shown in Box 6.1.

Recent data from public mental health systems in the US show that the leading cause of early death amongst people with serious mental illness is cardiovascular disease (CVD); combining heart disease and cerebrovascular disease, CVD was responsible for roughly 35% of deaths in this population. Suicide, by contrast, was responsible for fewer than 5% of deaths⁵.

Cardiovascular disease

Cardiovascular disease accounts for over 50% of all deaths in the US general population¹¹. Patients with schizophrenia are even more likely to have cardiovascular disease, and this is the leading cause of mortality in schizophrenia patients^{5,12–14}. Goff et al¹⁵, comparing schizophrenia patients from the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) trial to matched controls from National Health and Nutrition Examination Survey (NHANES) III, reported that schizophrenia patients had a significantly higher 10-year risk of coronary heart disease than matched controls. A recent retrospective cohort study comparing 3022 individuals with schizophrenia with a general

Box 6.1 Disease-specific standardized mortality ratios in 370 schizophrenia patients¹⁰.

Any cancer	1.46
Lung cancer	2.08
Cardiovascular disease	1.87
Circulatory diseases	2.49
Cerebrovascular disease	5.34
Diseases of the nervous system	6.14
Diabetes mellitus	9.96
Endocrine diseases	11.66
Respiratory diseases	3.19
Epilepsy	26.13

population cohort found the prevalence of cardiovascular disease was increased in schizophrenia (10.6% versus 8.7%), along with the incidence of ventricular arrhythmia (odds ratio (OR) 2.3, 95% confidence interval (CI) 1.2–4.3), stroke (OR 1.5, 95% CI 1.2–2.0), diabetes (OR 1.8, 95% CI 1.2–2.6), and heart failure (OR 1.6, 95% CI 1.2–2.0)¹².

Diabetes mellitus

The prevalence of type 2 diabetes mellitus is estimated to range from two to four times higher in schizophrenia patients than in the general population (15–18% versus around 4% of the general population)^{16–19}. Furthermore, schizophrenia is associated with an increase in the incidence of diabetes in earlier adult years^{20,21}.

While limited data from drug-naïve schizophrenia patients suggest that increased activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system may contribute to the onset or worsening of diabetes in patients with schizophrenia²², the finding of increased adiposity or glucoregulatory impairments in unmedicated patients is not consistently observed²³, and HPA activation is only variably associated with schizophrenia and largely reduced by antipsychotic treatment. Genetic and/or familial factors might play a role, as around one-fifth of schizophrenia patients have a family history of type 2 diabetes mellitus¹⁶; however, it remains to be seen to what extent the increased prevalence of diabetes in this population cannot be fully explained by increases in the prevalence of overweight and obesity as well as reductions in level of fitness²⁴.

Infectious disease

In developing countries, infectious diseases remain a pressing issue for individuals with schizophrenia. In industrialized nations, these are a less important cause of morbidity and mortality, though rates of infectious disease among patients with schizophrenia are higher than in the general population¹. For example, rates of HIV infection are increased eightfold in patients with a severe mental illness, and data have shown that knowledge of exposure risks is generally low among patients²⁵. Rates of hepatitis C infection are also elevated among those with a severe mental illness²⁵.

Cancer

The association between schizophrenia and risk of cancer has been of increasing interest and debate. While some studies have emphasized an increased

risk of cancer associated with schizophrenia, others have suggested that schizophrenia could provide a protective effect with respect to some cancers. While there is variability in available data and analytic approach, schizophrenia has generally been associated with a higher risk of cancer-related morbidity and mortality^{26,27}. A major analytic issue for surveys in this area is that increases in premature cardiovascular mortality in persons with schizophrenia⁵ may greatly reduce the probability of living long enough to develop many cancers.

Pulmonary disease

In one sample population of outpatients with severe mental illnesses, including schizophrenia, the prevalence of chronic obstructive pulmonary disease (COPD) was 22.6%²⁸. In addition, people with schizophrenia are more than twice as likely as the general population to develop asthma³. Abdominal adiposity can be hypothesized to contribute to the risk of COPD; however, smoking is the strongest independent risk factor for COPD, accounting for 60% of all smoking-related deaths. People with serious mental illnesses, including individuals with schizophrenia, are more than twice as likely to smoke as the general population, and are also more likely to be exposed to the effects of secondhand smoke²⁹. In a sample of 200 patients with schizophrenia, 17.8% had a lifetime history of asthma, 20.1% had a lifetime history of chronic bronchitis, and 8.1% had a lifetime history of emphysema^{3,28,30}.

Modifiable risk factors in people with schizophrenia

An important consideration in any effort to understand and address the excess mortality observed in individuals with schizophrenia is the increased prevalence of key modifiable risk factors for medical disease, and the low utilization of prevention approaches with established effectiveness in the general population. Key risk factors for major causes of mortality that form the basis of public health efforts in the general population are shown in Box 6.2.

Obesity

Obesity is approximately twice as prevalent in people with severe mental illnesses such as schizophrenia^{24,32}. In one analysis, a total of 73% of all schizophrenia patients were overweight, while 86% of the women with schizophrenia were either overweight or obese³⁰. Patients with schizophrenia

Box 6.2 Key modifiable risk factors for major causes of mortality³¹.

Overweight and obesity
 Smoking
 Hypertension
 Dyslipidemia
 Hyperglycemia

may be at higher risk of becoming obese due to a constellation of clinical, physiological, genetic, psychosocial, and environmental factors. Importantly, there is substantial evidence that treatment with some antipsychotic medications can induce substantial increases in weight and adiposity^{9,33–37}. In particular, drugs with greater antagonism for histamine (H₁) receptors, and to a lesser extent α_1 -adrenoceptors, have been associated with greater degrees of antipsychotic-induced weight gain³⁸. Rates of clinically significant weight gain associated with the atypical antipsychotics are shown in Box 6.3 (according to pooled registration trial data reported in the US package inserts^{33,34}).

Given the differential weight gain associated with different antipsychotic medications, reductions in weight can be hypothesized to occur with a switch from a high weight gain drug to a lower weight gain drug³⁴. Indeed, this effect

Box 6.3 Weight gain associated with atypical antipsychotics.**Increase of $\geq 7\%$ of body weight**

olanzapine: 29% (versus 3% for placebo)
 quetiapine: 23% (versus 6% for placebo)
 risperidone: 18% (versus 9% for placebo)
 ziprasidone: 10% (versus 4% for placebo)
 aripiprazole: 8% (versus 3% for placebo)

Mean weight gain over 1 year of treatment

olanzapine: 12 kg of weight gain at doses from 12.5 to 17.5 mg/day³⁹
 quetiapine: 3.2 kg⁴⁰ (note: based on an 'observed case' analysis, in contrast to the 'last observation carried forward' method used for the other medications)
 risperidone: 2.2 kg
 ziprasidone approximately 1 kg
 aripiprazole approximately 1 kg³³

has been observed in short-term clinical trials involving both aripiprazole and ziprasidone³³. In a recent longer-term study, patients were switched to ziprasidone from risperidone, olanzapine, or a first-generation antipsychotic. After 52 weeks of treatment with ziprasidone, patients switched from olanzapine had lost a mean 9.8 kg of weight compared with 6.9 kg in those switched from risperidone⁴¹. In phase 2 of the CATIE study, patients switched to ziprasidone from other atypical antipsychotics lost a mean 3.7 kg per month⁴².

Hypertension

Estimates of the rate of hypertension in schizophrenia patients range from 19%^{1,43} to 27%¹⁵, compared with an estimated rate of 15% in the general population^{43,44}. Increases in adiposity and insulin resistance are associated with increased sympathetic nervous system activity and sodium retention, and increasing risk for hypertension⁴⁵. Factors that contribute to obesity and insulin resistance in patients can therefore contribute to the risk for hypertension, including medications associated with weight gain^{38,46,47}.

Dyslipidemia

Dyslipidemia is a key risk factor for cardiovascular disease. Increased adiposity, independent of the cause, is associated with increased prevalence of dyslipidemia. In a study of patients with schizophrenia⁴⁸, 31% had serum triglyceride levels of more than 1.7 mmol/l. In addition, 58% of men had serum high density lipoprotein (HDL) cholesterol levels below 1 mmol/l, and 25% of women had HDL cholesterol levels below 1.2 mmol/l.

Some antipsychotic medications are associated with clinically significant increases in lipid parameters, generally in proportion to their association with weight gain^{9,33–36,49,50}. In CATIE phase 1, olanzapine was associated with the greatest increase in lipid parameters from baseline. Olanzapine-treated patients experienced a mean triglyceride increase of 42.9 ± 8.4 mg/dl and a mean increase in total cholesterol of 9.7 ± 2.1 mg/dl, compared with mean decreases of 18.1 ± 9.4 mg/dl and 9.2 ± 5.2 mg/dl, respectively, in for example ziprasidone-treated patients³⁷. In CATIE phase 2, patients switched to ziprasidone from other atypical antipsychotics showed mean decreases in triglycerides of 19.3 ± 10.3 mg/dl, and mean decreases in total cholesterol of 9.0 ± 3.5 mg/dl⁴²; this is consistent with the effect of removing the prior treatments, rather than indicating any direct lipid-lowering effect of this agent.

Insulin resistance and hyperglycemia

In patients with schizophrenia, the prevalence of insulin resistance has been estimated at 1.5–2.0 times that of the general population¹⁸. When patients with hyperglycemia progress to type 2 diabetes mellitus, they are at greater risk for increased morbidity and mortality due to acute metabolic complications, as well as chronic vascular disease⁹. Antipsychotic medications are associated with differing levels of risk for hyperglycemia, generally proportional to their association with weight gain^{9,33–36,49,50}. In CATIE phase 1, plasma glucose levels increased by a mean 15.0 ± 2.8 mg/dl in olanzapine-treated patients, compared with 2.3 ± 3.9 mg/dl in ziprasidone-treated patients³⁷.

While antipsychotics confer most of their associated risk through weight gain, evidence from controlled studies suggests the existence of some adiposity-independent antipsychotic-related treatment effects on blood glucose and insulin resistance^{35,51}. While most treatment-induced insulin resistance arises from increased abdominal adiposity secondary to antipsychotic-induced weight gain, it may also be caused by direct activity of antipsychotics, e.g. their effect on glucose transporter function⁵².

Metabolic syndrome

The key elements that compose the metabolic syndrome are shown in Box 6.4. These are also the major risk factors for type 2 diabetes mellitus and cardiovascular disease⁹. The prevalence of metabolic syndrome in patients with schizophrenia ranges from 37% to 46%, compared with approximately 25% in the adult US population^{54,55}. McEvoy and colleagues compared the baseline presence of metabolic syndrome components from the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) Trial with an age-matched general population sample from NHANES; and found that patients

Box 6.4 Elements of the metabolic syndrome.

Waist circumference (obligatory criterion)	Male ≥ 94 cm, Female ≥ 80 cm
PLUS at least two of the following	
blood pressure	$\geq 130/85$ mmHg
high-density lipoprotein (HDL)	Male >40 mg/dl, Female >50 mg/dl
triglycerides	≥ 150 mg/dl
fasting glucose	≥ 100 mg/dl

in the CATIE population had an elevated prevalence of these components compared to age-matched NHANES controls⁵³.

Antipsychotic medications are associated with development of the metabolic syndrome to differing degrees, again in proportion to their association with weight gain^{9,33–36,49,50}. Pooled data from two 26-week randomized double-blind trials, one comparing aripiprazole with placebo⁵⁶ and the other comparing aripiprazole with olanzapine⁵⁷, showed an incidence of metabolic syndrome of $19.2 \pm 4.0\%$ for olanzapine, $12.8 \pm 4.5\%$ for placebo, and $7.6 \pm 2.3\%$ for aripiprazole⁵⁸.

Smoking and substance abuse

Up to 81% of people with schizophrenia are addicted to nicotine through cigarettes, compared with 28% of the general population^{3,30,59,60}. There are also significantly more heavy cigarette users among schizophrenia patients, with 61% of men with schizophrenia and 42% of women with schizophrenia inhaling more than 20 cigarettes per day, compared with 15% of men and 11% of women in the general population ($p > 0.001$)¹⁰. In the CATIE Trial, 68% of patients were nicotine dependent⁶¹. Among 233 dual-diagnosis individuals with serious mental disorders (including schizophrenia) and substance use, 82% were classified as alcohol abusers⁶². In another analysis of dual-diagnosis patients with schizophrenia, 71% were documented as stimulant users. Patients with schizophrenia and concomitant substance use disorders have higher adjusted odds for heart disease, asthma, gastrointestinal disorders, skin infections, and respiratory disorders than patients with schizophrenia who do not abuse substances⁶³.

Primary and secondary prevention

There are substantial opportunities to improve primary and secondary prevention in individuals with schizophrenia. In a study by McCreddie et al, 19% and 28% of the women and men, respectively, had a coronary heart disease risk that was $>15\%$, a risk threshold at which treatment of dyslipidemia with a statin would be considered a valuable intervention^{17,30}. In the CATIE study, 88% of those patients with dyslipidemia were receiving no lipid lowering therapy, and 62% of patients with hypertension were receiving no antihypertensive agent⁶⁴. Druss et al⁶⁵ studied a national cohort of 88 241 Medicare patients 65 years of age and older, and found that patients with a mental illness were significantly less likely to receive reperfusion therapy post myocardial infarction, or treatment with aspirin, an angiotension converting enzyme (ACE)

inhibitor, or a beta-adrenergic antagonist⁶⁵. A study of approximately 300 000 individuals with diabetes from the Veteran Health Authority, with about 25% of the sample having a mental health condition, indicated significantly decreased odds of appropriate monitoring and control of diabetes and dyslipidemia in patients with psychotic disorders and other mental health conditions⁶⁶.

These data indicate a pervasive under-utilization of primary and secondary prevention approaches in patients with schizophrenia. Lack of timely recognition of medical conditions by physicians combined with patient non-compliance contribute to the higher mortality rates seen in these patients^{10,67}. Although there is no singular optimal model for healthcare delivery to the mentally ill, one proposed model suggests creating an integrated clinic in which medical care providers are on site and continually communicating with treating psychiatrists. This approach has been documented to improve medical outcomes without increasing total costs. Such an approach will increase primary prevention as well as diagnostic and treatment programs that specifically target patients with major mental illnesses⁶⁸. The role of the psychiatrist may involve coordination of medical care with a patient's primary care physician^{15,69}. Whatever model is adopted, patient education is a key component: a suggested patient education proforma is shown in Box 6.5.

During an initial visit between a treating psychiatrist and a patient, it is important that results of the most recent physical examination are reviewed.

Box 6.5 Educational tips for patients regarding physical health⁷⁰.

People with a mental illness are at increased risk for a number of medical conditions that can have a negative impact on quality of life and longevity. Also, some psychiatric medications have side-effects that can increase the risk of certain medical conditions, notably heart disease. It is very important for people with a mental illness to be aware of these issues and to ensure that their physical health is monitored and any problems appropriately treated.

Discuss these issues with your doctor and make sure you keep a record of your weight, waist measurement, and blood pressure.

Your doctor should arrange regular blood tests for you, the frequency depending upon your particular risk factors as well as the medication you are on. Tests include:

- fasting blood sugar (for diabetes)
- fasting blood fats ('lipid profile')
- liver function
- kidney function

METABOLIC SCREENING AND MONITORING FORM

NAME: _____

There is a growing awareness that some psychiatric illnesses and atypical antipsychotics can increase metabolic risks. Frequency of monitoring for modifiable risk factors depends on level of risk present at baseline screening.

OBESITY SCREENING ^{71,72}		Baseline		Dates/values from subsequent visits					
Consider BMI (weight/height in kg/m ²) at each visit. Normal (18.5–24.9); Overweight (25–29.9); Obese (≥30)		Height	Date	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___
		BMI	_____	_____	_____	_____	_____	_____	_____
		Wt	_____	_____	_____	_____	_____	_____	_____

LIPID SCREENING – CHOLESTEROL, TRIGLYCERIDES (TG) ⁷³					Baseline		Dates/values from subsequent visits					
	Optimal/ desirable (mg/dl)	Near/Above optimal (mg/dl)	Borderline high (mg/dl)	High/ undesirable (mg/dl)	Very high (mg/dl)	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	
Total	<200		200–239	≥240								
LDL	<100	100–129	130–159	160–189	≥190							
HDL	≥60			<40		Enter values as indicated in the Metabolic syndrome (MS) screening section of the form below.						
TG	<150		150–199	200–499	≥500*							

*≥500 for TG requires immediate pharmacotherapeutic intervention without waiting for therapeutic lifestyle changes.

METABOLIC SYNDROME (MS) SCREENING ⁷³		Baseline		Dates/values from subsequent visits					
Risk criteria		___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___
Abdominal obesity measured in waist circumference (men >40 inches, women >35 inches)									
Triglycerides (mg/dl) (≥150; or drug treatment)									
HDL cholesterol (mg/dl) (men <40, women <50; or drug treatment)									
Blood pressure (mmHg) (≥130/≥85; or drug treatment)									
Fasting plasma glucose (≥100 mg/dl; or drug treatment) ⁷⁴									
Total criteria for each visit (≥3 = MS diagnosis*)									

*Risk for cardiovascular disease increases with each criterion present, motivating intervention for any single criterion.⁷⁵

TYPE 2 DIABETES MELLITUS (T2DM) SCREENING ⁷¹		Baseline		Dates/values from subsequent visits						
Risk factors:		☐ Age (≥45)	☐ Overweight (BMI ≥25 kg/m ²)†	☐ Family history						
		☐ Habitual physical inactivity	☐ History of GDM or delivery of baby >9 lbs	☐ Previously identified IFG or IGT						
		☐ Race/ethnicity*	☐ Hypertension (>140/90 mmHg in adults)	☐ HDL ≤35 mg/dl and/or triglyceride ≥250 mg/dl						
		☐ Polycystic ovary syndrome	☐ History of vascular disease							
Diagnostic criteria for prediabetes and T2DM⁷¹		___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	
Fasting plasma glucose (FPG)§ Normal: <100 mg/dl; prediabetes: 100–125 mg/dl; T2DM: ≥126 mg/dl										
Two-hour postload glucose (OGTT)§ Normal: <140 mg/dl; prediabetes: 140–199 mg/dl; T2DM: ≥200 mg/dl										
Symptoms of T2DM (yes + casual (random) PG ≥200 mg/dl)¶										
Random plasma glucose (≥100 mg/dl requires formal screening with FPG or OGTT) ⁷⁶										

* Includes African Americans, Hispanic Americans, Native Americans, Asian Americans, Pacific Islanders.

† May not be correct for all ethnic groups.

‡ Screen at 3-year intervals beginning at age 45, particularly for those with BMI of ≥25; test at <45 or more frequently when overweight and have 1+ other risk factors.⁷¹

§ FPG and OGTT are the only measures currently approved by the ADA for diabetes screening/diagnosis; ADA recommends preferential use of FPG due to ease of use/acceptance.⁷¹

¶ Diagnosis must be confirmed on a subsequent day with FPG, 2-h PG, or casual (random) PG if symptoms (e.g. polyuria, polydipsia) are present, unless unequivocal hyperglycemia with acute metabolic decompensation is present.⁷¹

ATP-III recommends therapeutic lifestyle changes (TLC) for those with prediabetes,⁷⁷ hypertension,⁷⁸ 0–1 CHD risk factor and LDL ≥160 mg/dl,⁷⁹ 2+ CHD risk factors and LDL ≥130⁷³ MS;⁷³ and perhaps subsyndromal MS.⁷³ Follow-up monitoring of 6- to 12-week intervals to monitor TLC response⁷³ is recommended and pharmacotherapy intervention if TLC fails after 3 months – unless lipid, blood pressure, or glucose values demand immediate drug treatment.⁷³

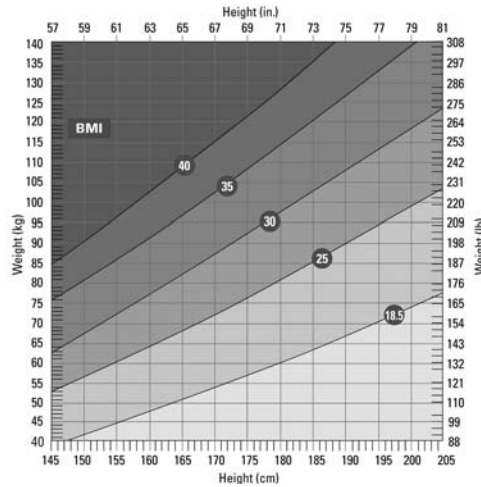
ADA/APA Consensus Statement recommends considering antipsychotic medication switch for those who gain ≥5% of baseline body weight.⁷⁹

Authored by John W. Newcomer, MD and Dan W. Haupt, MD. Compiled primarily from ADA and ATP-III guidelines.

©2006 Compact Clinicals

Produced by Compact Clinicals Kansas City, MO

Figure 6.1 An example of a metabolic screening form for tracking cardiometabolic risk in psychiatric patients. BMI, body mass index; HDL, high density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ADA, American Diabetes Association; CHD, coronary heart disease. Compact Clinicals. 7205 NW Waukomis Drive, Kansas City, Missouri 64151. 800-408-883. www.compact clinicals.com. 2006 Compact Clinicals. Kansas City, MO.

Body Mass Index Table Adapted from NHLBI Clinical Guidelines⁴⁵.**Note:** The table does not take into account age, sex, or ethnicity.**Figure 6.1**, *cont'd*

If such records do not exist, a medical screening should be arranged. Drug-naïve patients initiating antipsychotic therapy, as well as those changing antipsychotic treatment, should have a baseline assessment of family and personal medical history, as well as metabolic risk indicators such as weight (body mass index) and/or waist circumference, blood pressure, fasting plasma glucose, and fasting lipid measurements (total, low density lipoprotein (LDL) and HDL cholesterol, and triglyceride), and possibly glycosylated hemoglobin (HBA_{1C}), with repeat measurements of weight at every visit thereafter. The overall panel of laboratory indicators should be repeated at least 3 months into initial treatment and at least annually thereafter, or more often in the setting of increased risk¹⁸. A longitudinal tracking system is shown in Figure 6.1.

According to feedback from patients with schizophrenia who were being treated for comorbid type 2 diabetes mellitus, more of these individuals were satisfied with their lives than patients with the same comorbid status who were not receiving treatment for diabetes¹⁶. Thus, it is likely that concern for the physical health of schizophrenia patients will also increase the effects of, and compliance with, psychiatric treatment. In addition, behavioral therapy can be an effective method for overweight or obese patients with schizophrenia to manage unwanted weight gain⁸⁴.

INSTRUCTIONS FOR PHYSICIANS — Metabolic Screening And Monitoring Form

Obesity screening

Overweight and obesity predispose patients to coronary heart disease (CHD), stroke, and a variety of other medical conditions, and are associated with an increase in all-cause mortality⁹⁰. Overweight and obesity increase the risk of additional CHD risk factors, including:

- Type 2 diabetes mellitus (T2DM)
- Hypertension
- Dyslipidemia (e.g. increased low density lipoprotein (LDL) cholesterol and triglycerides (TG), and decreased high density lipoprotein (HDL) cholesterol)

Using the Body Mass Index Table on the back of the form*, determine BMI at baseline and subsequent visits to determine whether a patient's BMI falls within the 'Normal', 'Overweight', or 'Obese' range. Although some individuals with high BMIs have normal body fat and increased muscle mass, most individuals with BMIs above 25 have excess body fat.

Alternate BMI thresholds have been proposed for Asian Americans (e.g. onset of overweight/obesity at a BMI of 23/25). The BMI Table is also included on the inside of the back cover of the tear pad.

Lipid screening

The National Cholesterol Education Project (NCEP) recommendations focus on preventing CHD, metabolic syndrome (MS), and T2DM through preventive strategies that target primary prevention risk factors, including elevated LDL cholesterol⁷³.

CHD risk factors that guide NCEP treatment goals include:

- Cigarette smoking
- Hypertension (BP >140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dl)
- Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)
- Age (men >45 years; women >55 years)

Risk assessment begins with a fasting lipoprotein profile (total cholesterol, LDL, HDL, and TG) at 5-year intervals for adults aged >20 years. More frequent monitoring and risk-reduction interventions are initiated based on risk level.

This section of the form presents the range of values by category of risk (optimal/desirable to very high) as well as space to record baseline measurements and those taken on subsequent visits. Alert values, such as TG ≥500 mg/dl, may require immediate pharmacotherapeutic intervention without a trial of therapeutic lifestyle changes (TLC) alone.

Guidelines are indicated for HDL and TG, but these values are recorded in the space provided under Metabolic Syndrome (MS) Screening.

For more information on determining risk of CHD using lipid and non-lipid risk factors, see the full NCEP report⁷³.

Metabolic syndrome screening

Metabolic syndrome (MS) is a constellation of lipid and non-lipid risk factors of metabolic origin, closely related to each other via insulin resistance.

Associated features of MS include:

- Abdominal obesity
- Atherogenic dyslipidemia (elevated TG, small LDL particles, low HDL cholesterol)
- Raised blood pressure
- Insulin resistance (with or without glucose intolerance)
- Prothrombotic and proinflammatory states

For this portion of the form, fill in the individual values, and total the number of out-of-range results at the bottom of each column. ATP III recommends a diagnosis of MS when three or more of the risk determinants shown are present⁷³. However, it is worth noting that CHD risk can increase with one or two MS criteria⁷⁵.

Type 2 diabetes mellitus screening

The factors presented in the form reflect those that increase the risk of developing T2DM^{71,73,75}. *Note:* the presence of mental disorders, including schizophrenia and depression, has been associated with increased risk^{81,82}.

The American Diabetes Association (ADA) recommends that screening should be considered at 3-year intervals beginning at age 45, particularly in those with BMI ≥25. Screening should be considered at an earlier age and more frequently in those who are overweight if additional diabetes risk factors are present^{71,81}. Because some mental disorders and treatment have been associated with an increased risk of diabetes, clinicians should incorporate these risk factors into the determination of testing frequency^{71,81}.

The ADA recommends that screening for diabetes be performed using fasting plasma glucose (FPG) or an oral glucose tolerance test (OGTT). Of these recommended tests, the FPG is the easiest, fastest, and most convenient, but is less sensitive. The OGTT is more sensitive but more time consuming and costly to administer. If symptoms of T2DM are present, conduct a casual (random) glucose test to see if patient meets T2DM diagnostic criteria (casual plasma glucose ≥200 mg/dl). Note that diagnosis must be confirmed on a subsequent day with FPG, 2-h PG, or casual plasma glucose with symptoms, unless unequivocal hyperglycemia with acute metabolic decompensation is present.

Although not ADA recommended, some groups support the use of a casual (random) plasma glucose for screening, recommending that a value of ≥100 mg/dl be followed by formal screening with FPG or OGTT⁷⁶.

References are located on the back of the Metabolic Screening and Monitoring Form.

Figure 6.1 *cont'd*

Conclusions

Schizophrenia is frequently accompanied by medical comorbidities such as cardiovascular disease, cancer, and diabetes, in addition to other prevalent complications including substance use¹⁻⁴. Therefore, addressing the risk and treatment of comorbidities is essential to improving health outcomes among patients in this population. Psychiatric and medical care systems have a particular responsibility to address those components of risk that are iatrogenic in origin, e.g. the contribution of medication side-effects. The Institute of Medicine suggests that all psychiatric and medical systems and their associated providers involved in the care of patients with schizophrenia – including mental health, substance use, general health care, and other services – need to collaborate effectively in an effort to co-ordinate care of their patients⁸⁵. This co-operation should include the establishment of structured and routine comorbidity risk assessments for patients, in addition to scheduled monitoring of antipsychotic treatment for side-effects and adherence issues⁸⁵. Implementation of such screening before the initiation of antipsychotic treatment and during therapy will likely improve outcomes among individuals with schizophrenia.

Declaration

JW Newcomer has research grants from The National Institute of Mental Health, The National Alliance for Research on Schizophrenia and Depression, Sidney R. Baer Jr. Foundation, Janssen, Bristol-Myers Squibb, Wyeth, and Pfizer Inc.; he has been a consultant to AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Pfizer Inc., Organon, Solvay, and Wyeth; he has been a legal consultant to litigation; and he has received royalties from Compact Clinicals for a metabolic screening form.

Acknowledgment

We would like to thank Glennon M Floyd for editorial assistance with this chapter.

References

1. Dixon L, Postrado L, Delahanty J et al. The association of medical comorbidity in schizophrenia with poor physical and mental health. *J Nerv Ment Dis* 1999; 187: 496–502.
2. Lyketsos CG, Dunn G, Kaminsky MJ et al. Medical comorbidity in psychiatric inpatients: relation to clinical outcomes and hospital length of stay. *Psychosomatics* 2002; 43: 24–30.

3. Sokal J, Messias E, Dickerson FB et al. Comorbidity of medical illnesses among adults with serious mental illness who are receiving community psychiatric services. *J Nerv Ment Dis* 2004; 192: 421–7.
4. Goldman LS. Medical illness in patients with schizophrenia. *J Clin Psychiatry* 1999; 60 (Suppl 21): 10–15.
5. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis* 2006; 3: A42.
6. Osby U, Correia N, Brandt L et al. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophr Res* 2000; 45: 21–8.
7. Druss BG, Rosenheck RA. Use of medical services by veterans with mental disorders. *Psychosomatics* 1997; 38: 451–8.
8. Jeste DV, Gladsjo JA, Lindamer La et al. Medical comorbidity in schizophrenia. *Schizophr Bull* 1996; 22: 413–30.
9. Casey DE, Haupt DW, Newcomer JW et al. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. *J Clin Psychiatry* 2004; 65: 4–18.
10. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. *Br J Psychiatry* 2000; 177: 212–17.
11. Rosamond W, Flegal K, Friday G et al. Heart disease and stroke statistics – 2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2007; 115: e69–171.
12. Curkendall SM, Mo J, Glasser DB et al. Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. *J Clin Psychiatry* 2004; 65: 715–20.
13. Osborn DP, Levy G, Nazareth I et al. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's general practice research database. *Arch Gen Psychiatr* 2007; 64: 242–9.
14. Miller BJ, Paschall CB, Svendsen 3rd DP. Mortality and medical comorbidity among patients with serious mental illness. *Psychiatr Serv* 2006; 57: 1482–7.
15. Goff DC, Sullivan LM, Mcevoy JP et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res* 2005; 80: 45–53.
16. Dixon L, Weiden P, Delahanty J et al. Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophr Bull* 2000; 26: 903–12.
17. Wood D, Durrington P, Mcinnes G et al. Joint British recommendations on prevention of coronary heart disease in clinical practice. *Heart* 1998; 80: s1–s29.
18. Expert Consensus Group Schizophrenia and Diabetes 2003. Expert Consensus Meeting, Dublin, 3–4 October 2003: consensus summary. *Br J Psychiatry Suppl* 2004; 184 (suppl 47): S112–14.
19. Bushe C, Holt R. Prevalence of diabetes and impaired glucose tolerance in patients with schizophrenia. *Br J Psychiatry Suppl* 2004; 47: S67–71.
20. Harris MI. Diabetes in America: epidemiology and scope of the problem. *Diabetes Care* 1998; 21 (Suppl 3): C11–14.
21. Mukherjee S, Decina P, Bocola V et al. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry* 1996; 37: 68–73.
22. Ryan MC, Thakore JH. Physical consequences of schizophrenia and its treatment: the metabolic syndrome. *Life Sci* 2002; 71: 239–57.
23. Reynolds GP. Metabolic syndrome and schizophrenia. *Br J Psychiatry* 2006; 188: 86; author reply 86–7.
24. Allison DB, Fontaine KR, Heo M et al. The distribution of body mass index among individuals with and without schizophrenia. *J Clin Psychiatry* 1999; 60: 215–20.
25. Cournos F, Mckinnon K, Sullivan G. Schizophrenia and comorbid human immunodeficiency virus or hepatitis C virus. *J Clin Psychiatry* 2005; 66 Suppl 6: 27–33.

26. Grinshpoon A, Barchana M, Ponizoversusky A et al. Cancer in schizophrenia: is the risk higher or lower? *Schizophr Res* 2005; 73: 333–41.
27. Lichtermann D, Ekelund J, Pukkala E et al. Incidence of cancer among individuals with schizophrenia and their relatives. *Arch Gen Psychiatry* 2001; 58: 573–8.
28. Himelhoch S, Lehman A, Kreyenbuhl J et al. Prevalence of chronic obstructive pulmonary disease among those with serious mental illness. *Am J Psychiatry* 2004; 161: 2317–19.
29. National Association of State Mental Health Program Directors (NASMHPD) Medical Directors Council, Parks J, Jewell P, eds. Technical report on smoking policy and treatment in state operated psychiatric facilities. Twelfth in a series of technical reports, 2006. Available at <http://www.nasmhpd.org>.
30. McCreadie RG. Diet, smoking and cardiovascular risk in people with schizophrenia: descriptive study. *Br J Psychiatry* 2003; 183: 534–9.
31. National Cholesterol Education Program Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486–97.
32. Susce MT, Villanueva N, Diaz FJ et al. Obesity and associated complications in patients with severe mental illnesses: a cross-sectional survey. *J Clin Psychiatry* 2005; 66: 167–73.
33. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* 2005; 19 (Suppl 1): 1–93.
34. Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. *J Clin Psychiatry* 2007; 68 (Suppl 4): 8–13.
35. Newcomer JW, Haupt DW, Fucetola R et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry* 2002; 59: 337–45.
36. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; 27: 596–601.
37. Lieberman JA, Stroup TS, Mcevoy JP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*, 2005; 353: 1209–23.
38. Kroeze WK, Hufeisen SJ, Popadak BA et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology* 2003; 28: 519–26.
39. Nemeroff CB. Dosing the antipsychotic medication olanzapine. *J Clin Psychiatry* 1997; 58 (Suppl 10): 45–9.
40. Brecher M, Leong RW, Stening G et al. Quetiapine and long-term weight change: a comprehensive data review of patients with schizophrenia. *J Clin Psychiatry* 2007; 68: 597–603.
41. Weiden PJ, Newcomer JW, Loebel AD et al. Long-term changes in weight and plasma lipids during maintenance treatment with ziprasidone. *Neuropsychopharmacology* 2007; Epub ahead of print.
42. Stroup TS, Lieberman JA, Mcevoy JP et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry* 2006; 163: 611–22.
43. Hennekens CH, Hennekens AR, Hollar D et al. Schizophrenia and increased risks of cardiovascular disease. *Am Heart J* 2005; 150: 1115–21.
44. Hennekens CH. Increasing burden of cardiovascular disease: current knowledge and future directions for research on risk factors. *Circulation* 1998; 97: 1095–102.
45. Reaven G. Insulin resistance, hypertension, and coronary heart disease. *J Clin Hypertens* (Greenwich) 2003; 5: 269–74.
46. Allison DB, Mentore JL, Heo M et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; 156: 1686–96.

47. Henderson DC, Nguyen DD, Copeland PM et al. Clozapine, diabetes mellitus, hyperlipidemia, and cardiovascular risks and mortality: results of a 10-year naturalistic study. *J Clin Psychiatry* 2005; 66: 1116–21.
48. Heiskanen T, Niskanen L, Lyytikäinen R et al. Metabolic syndrome in patients with schizophrenia. *J Clin Psychiatry* 2003; 64: 575–9.
49. Haupt DW, Fahnstock PA, Flavin KA et al. Adiposity and insulin sensitivity derived from intravenous glucose tolerance tests in antipsychotic-treated patients. *Neuropsychopharmacology* 2007; in press.
50. Newcomer JW, Fahnstock PA, Haupt DW et al. Adiposity and hyperinsulinemic euglycemic clamp-derived insulin sensitivity in antipsychotic-treated patients. Submitted.
51. Houseknecht KL, Robertson AS, Zavadoski et al. Acute effects of atypical antipsychotics on whole-body insulin resistance in rats: implications for adverse metabolic effects. *Neuropsychopharmacology* 2007; 32: 289–97.
52. Haupt DW, Newcomer JW. Hyperglycemia and antipsychotic medications. *J Clin Psychiatry* 2001; 62 (Suppl 27): 15–26; discussion 40–1.
53. McEvoy JP, Meyer JM, Goff DC et al. Prevalence of the metabolic syndrome in patients with schizophrenia: Baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res* 2005; 80:19–32.
54. Park YW, Zhu S, Palaniappan L et al. The Metabolic Syndrome: Prevalence and Associated Risk Factor Findings in the US Population From the Third National Health and Nutrition Examination Survey, 1988–1994. *Arch Intern Med* 2003; 163: 427–36.
55. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. Adults. *Diabetes Care* 2004; 27: 2444–9.
56. Pigott TA, Carson WH, Saha AR et al. Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. *J Clin Psychiatry* 2003; 64: 1048–56.
57. McQuade RD, Stock E, Marcus R et al. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. *J Clin Psychiatry* 2004; 65 (Suppl 18): 47–56.
58. L'italien GJ. Pharmacoeconomic impact of antipsychotic-induced metabolic events. *Am J Manag Care* 2003; 3: S38–S42.
59. Holmberg SK, Kane C. Health and self-care practices of individuals with schizophrenia. *Psychiatr Serv* 1999; 50: 827–9.
60. Cormac I, Ferriter M, Benning R et al. Physical health and health risk factors in a population of long-stay psychiatric patients. *Psychiatric Bull* 2005; 29: 18–20.
61. Goff DC, Cather C, Evins AE et al. Medical morbidity and mortality in schizophrenia: guidelines for psychiatrists. *J Clin Psychiatry* 2005; 66: 183–94; quiz 147, 273–4.
62. Miles H, Johnson S, Amponsah-Afuwape S et al. Characteristics of subgroups of individuals with psychotic illness and a comorbid substance use disorder. *Psychiatr Serv* 2003; 54: 554–61.
63. Dickey B, Normand SL, Weiss RD et al. Medical morbidity, mental illness, and substance use disorders. *Psychiatr Serv* 2002; 53: 861–7.
64. Nasrallah HA, Meyer JM, Goff DC et al. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: data from the CATIE schizophrenia trial sample at baseline. *Schizophr Res* 2006; 86: 15–22.
65. Druss BG, Bradford WD, Rosenheck et al. Quality of medical care and excess mortality in older patients with mental disorders. *Arch Gen Psychiatry* 2001; 58: 565–72.
66. Frayne SM, Halanych JH, Miller DR et al. Disparities in diabetes care: impact of mental illness. *Arch Intern Med* 2005; 165: 2631–8.

67. Munk-Jorgensen P, Mors O, Mortensen PB. et al. The schizophrenic patient in the somatic hospital. *Acta Psychiatr Scand* 2000; 102: 96–9.
68. Davidson M. Risk of cardiovascular disease and sudden death in schizophrenia. *J Clin Psychiatry* 2002; 63 (Suppl 9): 5–11.
69. Daumit GL, Crum RM, Guallar E et al. Receipt of preventive medical services at psychiatric visits by patients with severe mental illness. *Psychiatr Serv* 2002; 53: 884–7.
70. Castle DJ, Tran N. *Psychiatric Medication Information: A Guide for Patients and Carers*. St Vincent's Mental Health, Melbourne, 2007.
71. American Diabetes Association. Screening for type 2 diabetes. *Diabetes Care* 2004; 27(suppl 1): S11–14.
72. Centers for Disease Control and Prevention. BMI- Body Mass Index: About BMI for Adults, Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion, 2006. Available at: http://www.cdc.gov/nccdphp/dnpa/bmi/adult_BMI/about_adult_BMI.htm. Accessed April 21, 2006.
73. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), Third report of the NCEP panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *Circulation* 2002; 106(25): 3143–421.
74. Grundy SM, Cleeman JI, Daniels SR et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: executive summary. *Circulation* 2005; 112: 1–6.
75. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of the Diabetes. *Diabetes Care* 2005; 28: 2289–304.
76. Lambert TJR, Chapman LH. Diabetes, psychotic disorders and antipsychotic therapy: a consensus statement. *Med J Aust* 2004; 181(10): 544–8.
77. American Diabetes Association, Standards of medical care in diabetes – 2006. *Diabetes Care* 2006; 29: S4–S42.
78. National Heart, Lung, and Blood Institute. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. NIH Publication No. 04-5230. August 2004.
79. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care* 2004; 27(2): 596–601.
80. Klein S, Wadden T, Sugerman HJ, AGA technical review on obesity. *Gastroenterology* 2002; 123: 882–932.
81. Canadian Diabetes Association Clinical Practice Guidelines Expert committee, Canadian Diabetes Association 2003 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2003; 27(suppl 2): S10–S13.
82. Lustman PJ, Anderson RJ, Freedland KE Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care* 2000; 23: 934–42.
83. National Institutes of Health, National Heart, Lung and Blood Institute, North American Association for the Study of Obesity. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. U.S. Department of Health and Human Services, Public Health Service; NIH Publication No. 98-4083; September 1998.
84. Brar JS, Ganguli R, Pandina G et al. Effects of behavioral therapy on weight loss in overweight and obese patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry* 2005; 66: 205–12.
85. Institute of Medicine. Improving quality of health care for mental and substance-use conditions. Washington, DC: The National Academies Press, 2006.

Substance abuse comorbidity in schizophrenia

Wynne James, Kim Mueser, and David J Castle

Research over the past 30 years has explored the prevalence and possible causes of substance misuse among people with schizophrenia, as well as highlighting some of the complications that can occur as a consequence. While these studies have significantly improved our understanding of the complex interplay between drug misuse and schizophrenia, only a small number of research studies have evaluated treatment interventions aimed at improving outcomes for this group.

This chapter discusses a number of important considerations essential for a clear understanding of the relationship between substance misuse and schizophrenia. These include prevalence, impact on the course of the illness, clinical implications, and reasons for use. We review studies addressing substance use in schizophrenia, provide a brief overview of a novel psychosocial treatment program aimed at directly addressing substance abuse in this population, and conclude by outlining medication strategies for people with schizophrenia and substance abuse.

It should be noted that cigarette smoking and caffeine abuse are also very common amongst people with schizophrenia¹, and these carry their own health risks. In this chapter, however, we concentrate on alcohol and illicit substances.

Prevalence

The prevalence of substance abuse among people with schizophrenia attracts considerable attention from service providers and researchers².

Box 7.1 Summary of weaknesses of prevalence studies of substance abuse in schizophrenia.

Lack of standardized instruments used to determine diagnosis
No consensus about 'caseness'
Research sampling procedures likely to reflect bias
Berkson's bias
Poor distinction between various degrees of substance use
Varying global patterns of drug use

However, studies in this area frequently suffer from a number of shortcomings, notably with respect to defining 'caseness' (see Box 7.1). This problem arises from the lack of standardized instruments used to determine diagnoses and for indexing degrees of substance use. Poor sampling procedures contribute by over-representing patients from urban areas, where substance use is often more prevalent. Berkson's bias also operates, in that the effect of coming to the attention of services consequent upon each individual disorder is additive, and results in higher rates of comorbidity than in non-clinical samples³.

There is also considerable variability in reported prevalence rates with respect to the different groups of drugs used, a fact easily obscured by use of umbrella terms such as 'drug abuse'. Different drugs have different physical and psychological consequences and any evaluation regarding treatment interventions should be as specific as possible about what works best with respect to each individual drug class. Finally, any results regarding prevalence rates are strongly influenced by local trends and the legal and social status of particular drugs in particular settings, making the generalizability of results questionable.

These issues aside, there is now a general consensus that substance use disorders occur more frequently among people with schizophrenia than in the general population. In a review of the international literature, Cantor-Graae et al⁴ found 47 studies recording prevalence of substance abuse/dependence amongst people with a psychotic illness since 1990. Of these, 37 were conducted in North America, eight in Europe, and one each in Australia and Africa. Rates of use varied widely, dependent upon the criteria applied and the setting, but lifetime rates for abuse of 'any substance' tended to aggregate around 40–60%. Alcohol and cannabis were the leading drugs in all settings; other drugs of abuse varied by setting. Polydrug abuse is also a feature of this clinical group; for example, Spencer et al⁵, in an Australian sample, found that around 50% of psychosis patients regularly used more than one substance.

Community studies give a less biased assessment of rates of substance use, and allow comparison with controls who do not have a mental illness. Perhaps the most frequently cited community prevalence study of mental disorders, the US Epidemiological Catchment Area Survey (ECA⁶), estimated that 47% of people with schizophrenia also met criteria for lifetime substance abuse or dependence. Around one-third of this group had a substance abuse disorder in the previous 6 months⁷. The lifetime rate of substance abuse in controls was around 17%. In the Australian Study of Low Prevalence (psychotic) Disorders¹, lifetime rates of substance abuse or dependence amongst people with psychotic disorders were 38.7% for males and 17.0% for females (compared with 9.4% and 3.7%, respectively, in the general population) for alcohol, and 36.3% for men and 15.7% for women (compared with 3.1% and 1.3% 12-month prevalence in the general population) for illicit substances. The most commonly abused illicit substance was cannabis, followed by amfetamines, lysergic acid diethylamide (LSD), heroin, and tranquilizers; 19.1% of the sample were using more than one drug. Of the sample 12% had wanted, but felt unable, to stop or cut down their substance use.

Impact of substance abuse on the course of schizophrenia

Whilst it has been shown in a number of studies that substance abuse often precedes the onset of psychotic symptoms in psychotic disorders^{8,9}, this does not imply causality; indeed, whether such substances can actually cause disorders such as schizophrenia is open to considerable conjecture¹⁰. What is generally accepted is that use of substances such as cannabis can precipitate psychotic episodes in vulnerable individuals¹¹. Furthermore, most studies (but not all⁴) report that substance abuse among people with psychotic disorders tends to be associated with a poorer illness trajectory. Substance abuse has been identified as a significant factor in contributing to an increase in the number of psychotic symptoms and relapses. This is especially so with respect to patients who abuse psychotogenic drugs such as cannabis and cocaine, with heavier use of these drugs correlating with a worse symptom profile¹². It is also the case that some patients with psychotic disorders who abuse substances have a better longitudinal course than their non-using counterparts if they stop using¹³. This again reinforces the need to assist people with a vulnerability to psychotic illnesses to gain control of, and limit, their use of alcohol and illicit substances.

Clinical implications

Substance abuse is positively correlated with poor treatment adherence and as a result is a contributing factor to the worse outcome observed in this clinical group¹⁴. Another major cause for concern among service providers and clinicians, is violence and crime (see Chapter 9). A number of studies have identified substance abuse as a significant risk factor for violence in people with psychotic disorders¹⁵. Cuffel et al¹⁶ found that polysubstance abuse among this group was associated with a significant increase in the likelihood of violent behaviors, including threats, destruction of property, assault, and suicide.

Prevalence rates for blood-borne viruses such as HIV are higher among people with psychotic disorders complicated by substance abuse¹⁷. These findings underscore the requirement for ongoing health education strategies that are sensitive to the needs of specific groups. Harm reduction interventions should be a priority for patients involved in high-risk activities such as intravenous drug use, and clinicians should be pro-active in delivering them.

Homelessness is another significant problem for this group¹⁸; this in turn complicates ongoing management by treatment services. Not surprisingly, rates of psychiatric hospitalization are high among people with substance abuse comorbidity¹⁹ and while inpatient psychiatric services remain an expensive and limited resource, this is a major concern for service providers.

Thus, it is clear that the use of alcohol and illicit substances has a negative impact on people with psychotic disorders. Box 7.2 summarizes these parameters. It is important to develop more effective methods of engaging such individuals in treatments that address their substance use.

Box 7.2 Clinical implications of substance abuse in schizophrenia.

- Result in increased positive symptoms
- Difficulty in maintaining stable housing
- Money management problems
- Blood-borne virus risk behavior
- Higher rates of violent behavior
- Higher rates of hospitalization

Motivations for substance use

Gaining a better understanding of motivations for substance use is an important first step in developing more effective treatments for people with psychotic disorders. This aspect of substance use is still poorly understood. The notion of 'self-medication' was for many years the predominant theory used to explain the higher rates of substance abuse among people with psychotic disorders²⁰. This hypothesis suggests that substance abuse is an attempt by the individual to deal with symptoms of their illness, or to counteract some of the unwanted side-effects attributed to psychiatric medications. While this theory cannot be discounted, recent studies have identified a number of other factors involved in the etiology of substance abuse among people with psychotic illnesses (Box 7.3).

In a study investigating motivations for use in people with psychosis (mainly schizophrenia), Spencer et al⁵ found that, while there was some evidence to confirm the notion of self-medication, many respondents attributed their substance use to the same motivations as those given by the general population. Thus, these subjects reported that their substance use was driven by negative emotions such as boredom and depression; social motives such as conformity and acceptance, and improving social interaction; and was seen by some as a way of enhancing mood. Another consideration lending support to these findings is that, as stated above, drug use among this group generally reflects local community drug trends, rather than there being a specific correlation between certain symptoms or side-effects, and use of certain drugs of abuse¹². It is probable that a number of factors contribute to the high rate of substance abuse in people with psychotic disorders, and that many of these

Box 7.3 Reasons for substance abuse by people with schizophrenia.

Self-medication: the relief of distressing symptoms and/or side-effects of medication

Enhancement: 'to make you feel good'

Social motives: 'it's what others do'

Coping with unpleasant affect: 'to forget your worries'

Conformity: 'not to be left out'

Acceptance: 'to be liked'

Changing moral attitudes towards drugs use

Increased availability

Community psychiatric care

factors are the same as those mediating abuse in patients without such disorders. Mueser et al²¹, for example, have suggested a multifactorial model with antisocial personality disorder and supersensitivity to substances of abuse being contributory factors. The challenge for the field is to establish treatments that are responsive to these motivations for use, such that patients can be engaged in a treatment that is relevant and responsive to their particular makeup and situation.

Treatments for substance use in psychosis

Whilst substance use is an acknowledged problem in mental health settings, it often goes undetected, and thus untreated. Part of the reason for this is the traditional dichotomy between substance misuse and mental health services, and also the lack of acceptable and well validated treatments²². Kavanagh²³, reviewing treatments for substance use and mental health comorbidity, concluded that it was preferable to develop such interventions as part of an integrated treatment approach. This implies incorporating aspects from both mental health and substance abuse treatments, and these being delivered simultaneously by the same personnel²⁴. Thus, treatments should be nested in clinical practice settings, and involve collaboration among different health professionals. This is often not the case in current clinical practice, and services are more often than not polarized, such that the substance-using person with a psychotic illness 'falls between the cracks'.

Furthermore, there remains a major deficit in terms of defining the most effective content, shape, and form of interventions which will assist people with substance use comorbidity to control their substance use. Drake et al²² reviewed published studies in the area. They found 36 relevant studies, including patients with an array of psychiatric disorders. Only four of the 36 studies assessed specific treatment groups as an addition to existing services: all had small numbers of participants, and a substantial drop-out rate, none incorporated a motivational element, none were controlled, and none used established outcome measures. Nine further studies evaluated intensive integrated treatments, which were multifaceted and very labor intensive (several hours per day for weeks to months); again there was a substantial drop-out, making formal evaluation difficult. A further 13 studies (four controlled) were part of the US Community Support Program (CSP), with a total of 1157 participants. These studies used heterogeneous interventions, and the interventions were often modified as they were being delivered,

making it impossible to assess which elements were effective. Few standardized measures were used, and statistical analyses were limited. Finally, ten studies (four controlled) assessed comprehensive integrated services; again the interventions were multifaceted, including intensive case management, assertive outreach, and individual counseling, precluding assessment of effective elements.

Thus, existing studies have notable methodological flaws, often entail very time-consuming and therapist-intensive interventions, and give little indication of precisely which elements of the intervention are effective (or not). Many of the strategies described are not practical to implement outside research settings and do not appear to be generalizable either across treatment settings (e.g. mental health and non-government services; early episode and chronic rehabilitation settings), or to patients at different stages of their illness (e.g. early episode, chronic). Furthermore, they are generally not informed by assessment of the motivations for use by the particular individual, preventing tailoring of the intervention to the individual patient. Finally, very few studies have undertaken adequate rigorous scientific evaluation of the intervention, using a controlled experimental design and validated assessment instruments.

Psychosocial treatments

Despite the flaws in the literature on treatment interventions for substance use in schizophrenia, there is growing consensus about what features such interventions should contain²⁵ (see Box 7.4).

Box 7.4 Content of psychosocial treatment interventions for substance abuse in schizophrenia. Based on Drake and Mueser²⁵.

Interventions congruent with readiness to change
 Not abstinence focused
 Psychoeducation
 Harm reduction interventions
 Motivation enhancement strategies
 Relapse prevention strategies
 Peer orientated
 Offers links to other supportive agencies

We provide here an outline of a group psychosocial treatment intervention for substance abuse in schizophrenia that incorporates many of these elements^{26,27}. This example illustrates many of the features currently advocated in the literature and draws from work undertaken by, amongst others, Marlatt and Gordon²⁸, Miller and Rollnick²⁹, Zeidonis and Fisher³⁰, Kavanagh³¹, Graham³², and Spencer et al⁵.

The intervention is delivered in an outpatient setting over a 6- to 8-week period and utilizes peer support, motivational enhancement strategies, relapse prevention, and harm minimization approaches. It is available as an adjunct to existing multidisciplinary case management services and is for people who have a psychotic condition and also use drugs. The group was designed with the following broad aims:

- to establish motivations for use, and tailor intervention strategies for individuals on the basis of these motivations;
- to provide a forum for participants to discuss the pros and cons of drug use;
- to provide up to date information to enable participants to make informed choices;
- to enhance motivation to reduce drug use or minimize associated problems;
- to encourage participants to develop ways of managing their symptoms, relieving boredom, or engaging in social activities without relying on drugs.

Importantly, there is the capacity to tailor the precise elements of the intervention to individuals within the group, based on and responsive to the factors that motivate their use of substances. This is accomplished through both exercises and examples used in the groups themselves, as well as being incorporated into the homework exercises that each participant is expected to complete. The group is divided into five modules, which can be completed in one or two sessions each. A more detailed description can be found in James et al²⁷.

A further influential study in this field is that of Barrowclough et al³³, who employed a comprehensive package incorporating motivational interviewing, cognitive behavioral treatment, and family/care giver intervention over a 9-month period. In a randomized trial against treatment as usual, there were modest improvements in general functioning and positive symptoms, and an increase in days abstinent from drugs. The applicability of this model to general health care settings remains to be evaluated.

Pharmacological strategies

Another element of treatment for comorbid substance use in schizophrenia is medication. Krystal et al¹³ have provided a useful guide to pharmacotherapy of such patients. They detail the importance of optimal treatment of symptoms and prevention of side-effects, to counter the 'self-medication' component of motivation for substance use. Their suggested strategies are detailed in Table 7.1.

Krystal et al¹³ also point out the potential for atypical antipsychotics (and clozapine in particular) to be associated with lower rates of substance misuse. They conjectured that this might be mediated by the particular receptor-binding profile of such agents, for example the blockade of serotonin 5HT₂ receptors (potentially decreasing impulsivity), and the relative tenacity for dopamine D1 and D4 receptors (perhaps diminishing novelty-seeking behaviors).

Another consideration is the use of anti-addiction agents such as naltrexone and acamprosate, but the literature is limited with respect to their use in schizophrenia patients. Disulfiram may have a limited role in people with schizophrenia, but compliance is often erratic and it can exacerbate psychotic symptoms¹³.

Table 7.1 Medication strategies to reduce 'self-medication' with non-prescribed substances by people with schizophrenia

<i>Symptom/side-effect</i>	<i>Therapeutic intervention</i>
Extrapyramidal side-effects	Lower dose of typical antipsychotic Use atypical antipsychotic
Persistent positive symptoms	Optimize control; consider clozapine
Enduring negative symptoms	Ensure not secondary to typical antipsychotic, depression, positive symptoms Consider atypical agent notably clozapine
'Emotional distress'	Antidepressant/benzodiazepine Mood stabilizer
Cognitive dysfunction	Atypical antipsychotic Lower dose of typical antipsychotic Reduce benzodiazepines and anticholinergics Switch to atypical agent

Adapted from Krystal et al.¹³

Conclusions

Substance abuse comorbidity in schizophrenia is a major problem both in terms of prevalence and the potential negative impact on illness course. Much needs to be done to enhance our understanding of what drives this comorbidity, and to refine therapeutic interventions.

References

1. Jablensky A, McGrath JJ, Herrman H et al. Psychotic disorders in urban areas: an overview of the Study on Low Prevalence Disorders. *Aust N Z J Psychiatry* 2000; 34: 221–36.
2. Mueser K, Yarnold P, Rosenberg S et al. Substance use disorder in hospitalised severely mentally ill psychiatric patients: prevalence, correlates and sub groups. *Schizophr Bull* 2000; 26: 179–92.
3. Fowler I, Carr V, Carter N et al. Patterns of current and lifetime substance use in schizophrenia. *Schizophr Bull* 1998; 24: 443–5.
4. Cantor-Graae E, Nordstrom LG, McNeil TF. Substance abuse in schizophrenia: a review of the literature and a study of correlates in Sweden. *Schizophr Res* 2001; 48: 69–82.
5. Spencer C, Castle D, Michie P. An examination of the validity of a motivational model for understanding substance use among individuals with psychotic disorders. *Schizophr Bull* 2002; 28: 233–47.
6. Regier D, Farmer N, Rae D et al. Comorbidity of mental disorders with alcohol and other drug abuse. *JAMA* 1990; 264: 2511–18.
7. Mueser KT, Bennet M, Kushner MG. Epidemiology of substance use disorders among people with chronic mental illness. In: Lehman AF, Dixon: LB (Eds) *Double Jeopardy: Chronic Mental Illness and Substance Use Disorders*. Harwood Academic Publishers, Switzerland, 1995.
8. Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. *Arch Gen Psychiatry* 1994; 51: 273–9.
9. Caspari D. Cannabis and schizophrenia: results of a follow-up study. *Eur Arch Psychiatr Clin Neurosci* 1999; 249: 45–9.
10. Arsenault L, Cannon M, Witton J et al. Cannabis as a potential causal factor in schizophrenia. In: D Castle, R Murray, eds. *Marijuana and Madness*. Cambridge, UK: Cambridge University Press 2004: 186–97.
11. Castle DJ, Ames FR. Cannabis and the brain. *Aust N Z J Psychiatry* 1996; 30: 179–83.
12. Dixon L. Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. *Schizophr Res* 1999; 35: 93–100.
13. Krystal JH, D'Souza CD, Madonick S et al. Toward a rational pharmacotherapy of comorbid substance abuse in schizophrenic patients. *Schizophr Res* 1999; 35: S35–S49.
14. Owen R, Fischer, E, Booth B et al. Medication noncompliance and substance abuse among patients with schizophrenia. *Psychiatr Serv* 1996; 47: 853–8.
15. RachBeisel J, Scott J, Dixon L. Co-occurring severe mental illness and substance use disorders: a review of recent research. *Psychiatr Serv* 1999; 50: 1427–33.
16. Cuffel BJ, Shunway M, Chouljian TL et al. A longitudinal study of substance use and community violence in schizophrenia. *J Nerv Ment Dis* 1994; 182: 704–8.

17. Carey M, Weinhardt L, Carey K. Prevalence of infection with HIV among the seriously mentally ill: review of research and implications for practice. *Prof Psychol Res Pr* 1995; 26: 262–8.
18. Drake R, Antosca L, Noordsy D et al. New Hampshire's specialised services for the dually diagnosed. *New Dir Ment Health Serv* 1991; 50: 57–67.
19. Bartels S, Teague G, Drake R et al. Substance abuse in schizophrenia: service utilisation and costs. *J Nerv Ment Dis* 1993; 181: 227–32.
20. Siegfried N. A review of comorbidity: major mental illness and problematic substance use. *Aust N Z J Psychiat* 1998; 32: 707–17.
21. Mueser KT, Drake RE, Wallach MA. Dual diagnosis: a review of etiological theories. *Addict Behav* 1998; 23: 717–34.
22. Drake RE, Mercer-McFadden C, Mueser KT et al. Review of integrated mental health and substance use treatment for patients with dual disorders. *Schizophr Bull* 1998; 24: 589–608.
23. Kavanagh D. Treatment of comorbidity project – National Workshop agenda papers. Canberra. Available from Department of Psychiatry, University of Queensland.
24. Ley A, McLaren S, Siegfried N. Treatment programmes for people with both severe mental illness and substance misuse (Cochrane Review). *Cochrane Library*, Issue 1 2001.
25. Drake R, Mueser K. Psychosocial approaches to dual diagnosis. *Schizophr Bull* 2000; 26: 105–18.
26. James W, Castle DJ. Addressing cannabis abuse in peoples with psychosis. In: D Castle, R Murray, eds. *Marijuana and Madness*. Cambridge University Press, Cambridge, 2004; pp. 186–97.
27. James W, Preston NJ, Koh G et al. A group intervention which assists patients with dual diagnosis reduce their drug use: a randomized controlled trial. *Psychol Med* 2004; 34: 983–90.
28. Marlatt G, Gordon J. *Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviours*. Guildford Press, New York, 1985.
29. Miller W, Rollnick S. *Motivational Interviewing: Preparing People to Change Addictive Behaviour*. Guildford Press, New York, 1991.
30. Ziedonis D, Fisher W. Assessment and treatment of comorbid substance abuse in individuals with schizophrenia. *Psychiatr Ann* 1994; 24: 477–83.
31. Kavanagh D. An intervention for substance abuse in schizophrenia. *Behav Change* 1995; 12: 20–30.
32. Graham HL. The role of dysfunctional beliefs in individuals who experience psychosis and use substances: implications for cognitive therapy and medication adherence. *Behav Cogn Psychother* 1998; 26: 193–208.
33. Barrowclough C, Haddock G, Tarrier N. Randomised controlled trial of motivational interviewing, cognitive behavior therapy, and family intervention for patients with comorbid schizophrenia and substance use disorders. *Am J Psychiatry* 2001; 158: 1706–13.

Management of acute behavioral disturbance in psychosis

David J Castle, Nga Tran, and Deirdre Alderton

This chapter outlines an approach to the management of acute behavioral disturbance in psychosis. It should be recognized at the outset that there are many different reasons for people with psychotic illnesses to become acutely behaviorally disturbed, and potentially violent to themselves or others. The management of such scenarios requires an evaluation of the factors that might be contributing, and, where possible, early intervention aimed at diffusing the situation prior to dangerous escalation.

‘Organic’ causes of acute behavioral disturbance

One often missed cause of acute behavioral disturbance in psychosis is the intercession of ‘organic’ factors, including head injury, metabolic and endocrine disturbances, and epileptic seizures. The patient might be experiencing an organic delirium, resulting in confusion, fear, and subsequent aggression. Intoxication with alcohol and illicit substances should be considered; withdrawal states (e.g. delirium tremens) might also be operating. Prescribed medications can also play a part here, e.g. anticholinergic delirium associated with agents such as chlorpromazine or benztropine, and withdrawal states associated with benzodiazepines. Recognition and treatment of the delirium is crucial in such cases, and merely administering further medications can compound rather than resolve the problem.

Delirium usually has an acute or subacute onset and a fluctuating course. The clinical features include¹:

- impaired attention;
- disorientation in time, place, and person;
- fluctuating concentration/attention span;
- rambling speech;
- emotional lability;
- worsening towards evening;
- visual hallucinations.

The management of delirium has been reviewed by Meagher², and includes identification and treatment of the underlying cause, ensuring safety of the individual and their environment, and optimizing environmental stimulation. Medications used in delirium should not be ones that might worsen the patient's mental state. In particular, antipsychotics with potent central anticholinergic properties (e.g. chlorpromazine) should probably be avoided. Haloperidol is widely used in clinical practice, in doses of 1–2 mg orally, intramuscularly, or intravenously, depending on clinical state; it is repeatable after 30 minutes if not initially effective².

A role for the atypical antipsychotics in the management of delirium will certainly evolve, given their relatively benign side-effect profile and lack of negative impact on cognition. Open case series of olanzapine (5–10 mg) and risperidone (1.5–4 mg) have attested to their successful use in delirium. A review of 13 studies of atypical antipsychotics in the treatment of delirium³ strongly supported the use of risperidone, olanzapine, and quetiapine in this setting. Olanzapine has intrinsic anticholinergic activity (see Chapter 1) and this may theoretically exacerbate delirium in some particularly susceptible patients, so should be closely monitored in such settings⁴. Both aripiprazole and amisulpride may be particularly useful and appropriate in the treatment of delirium in people with cardiac compromise, in light of their minimal effects on QTc interval^{5,6}. Further studies are required to elucidate the precise place of the particular atypical antipsychotics in managing delirium.

Benzodiazepines such as lorazepam (2–4 mg orally, or parenterally, every 4 hours) are particularly useful in deliria related to alcohol and other substances², but can aggravate other deliria and should be used with caution. Respiratory function should be monitored, particularly with parenteral use.

Acute behavioral disturbance in psychosis

In the absence of delirium, patients with psychotic disorders do have a propensity to acute behavioral disturbance under certain circumstances. In schizophrenia, the behavioral disturbance is often mediated by fear, as the patient may feel persecuted, or believe he/she is being followed and spied upon; thus, the intervention of police or mental health services can compound matters, and result in desperate acts of self-protection. In mania, the picture is different, with irritability and explosiveness often in response to apparently trivial events, or grandiose dismissiveness.

It is as well to recognize such factors, so that initial management does not serve to escalate matters. One should also be aware of those parameters associated with aggression in people with psychosis, as outlined in Box 8.1. Past aggression is probably the most powerful of all these predictors.

Signs of behavioral disturbance

Clinicians will come to recognize certain factors that are markers or predictors of imminent aggression in people with psychosis. These include pacing, agitation, angry gestures, closing of personal space, raised angry voice, and shouting. Verbal threats should always be taken seriously; one should be particularly wary if the patient is making specific threats towards a particular person, and consider that person withdrawing from the situation.

There is a gradation of acute behavioral disturbance from mild through moderate to severe. A useful approach is to grade the level of arousal using a standardized scale, such as that shown in Table 8.1. The virtue of this is that all staff can be using the same benchmarks, making assessment and communication easier, as well as guiding interventions and monitoring efficacy of

Box 8.1 Predictors of aggression in psychosis.

Young men
History of sociopathy/forensic history
Delirium, head injury
Alcohol intoxication
Illicit substance use
Psychosis, expressly if persecutory beliefs, command hallucinations
Past aggression/violence

Table 8.1 Acute arousal scale (based on ‘Patient Arousal Rating Scale’, Fremantle Hospital and Health Service)

<i>Grade of arousal</i>	<i>Severity and symptoms of arousal</i>
5	Highly aroused, violent towards self, others, or property
4	Highly aroused and possibly distressed or fearful
3	Moderately aroused, agitated, becoming more vocal, and unreasonable or hostile
2	Mildly aroused, pacing, still willing to talk reasonably
1	Settled, minimal agitation
0	Asleep or unconscious

Symptoms of ‘arousal’ include noisy, distressed, agitated, behavioral disturbance (increased motor activity, intrusive, disinhibited), verbally abusive, physically abusive (to self, others, or property), and fearful.

each particular intervention. This brief scale has been validated against the ‘gold standard’ but longer Positive and Negative Syndrome scale (PANSS) Excited Subscale, with excellent correlation ($\kappa = 0.83$)⁷.

Managing acute behavioral disturbance: non-pharmacological strategies

It is important to ensure that staff are well informed and feel safe – a fearful patient will be reassured by the sense that staff are calm and know what they are doing. It is crucial that consistent messages are given to the patient, so it is best to have a single nominated staff member who does the talking, and other attendant staff should be briefed as to what signal or words might indicate that physical restraint should be implemented, if required.

If possible the patient should be taken into an unstimulating environment, away from other patients, but staff should ensure that an exit can be accessed easily. Support staff should be close by, but unobtrusive. Anything that might be used as a weapon (e.g. pens, pagers, mobile phones) should be removed. The nominated staff member should talk in an even voice and not raise it. Speech should be slow and clear, other people present should be introduced, and everything that is going on should be explained. Sudden movements should be avoided. The patient should be reassured that the staff want to help him/her, and will try to work with them towards a mutually acceptable outcome⁸.

If physical restraint is required, then sufficient support staff should be close by and know what their role will be. Security personnel or the police should be called in where indicated, and should also be fully briefed about the clinical situation and what is expected of them. If possible, tasks for the restraint should be allocated ahead of time (e.g. arms, legs, and head) and a key word signaling the restraint to designated staff. Medications intended for administration should be drawn up in advance and the person to administer them selected. The patient should be talked to throughout, offering reassurance and explanation, and trying to obtain cooperation. Staff and the patient should be debriefed afterwards⁹.

The use of seclusion is somewhat controversial. It has been defined as ‘placement of a patient, alone, in a specially designated lockable room from which he or she can be observed through a window’¹⁰. Potential benefits of seclusion include control and safety for the individual, other patients, and staff; ‘time out’ in a low-stimulus environment; and as a way of avoiding excessive use of medication. There are downsides, including the potential for perception of seclusion as punitive, or a violation of patient’s rights¹¹. It can also reignite in the patient traumatic memories from their past, and arguably constitutes a traumatic event in itself.

Some centers have aimed for a ‘zero seclusion’ policy, and claim that this can be achieved without any increased risk to staff. The Pennsylvania State Hospital System’s Seclusion and Restraint Reduction Program resulted in a substantial decrease in the rates (from 4.2 to 0.3 episodes per 1000 patient-days) and duration (from 10.8 to 1.3 hours) of seclusion with no significant changes in rates of staff injuries¹². The elements of this program are shown in Box 8.2.

Box 8.2 Pennsylvania State Hospital System’s Seclusion and Restraint Reduction Program: six core strategies (National Executive Training Institute 2005).¹³

Leadership towards organizational change
 Using data to inform practice
 Workforce development
 Use of specific seclusion/restraint reduction tools
 Involvement of consumers
 Debriefing techniques

On balance, the judicious use of seclusion can, in our view, be a safe and effective adjunct to the management of the acutely behaviorally disturbed patient, but its use should be kept to a minimum and closely monitored. Also, a standardized debriefing process should be in place; this affords the opportunity for both staff and the patient to ventilate feelings about the event, to work through some of the associated negative emotions, and plan for how better to deal with such situations in the future, should they arise. An example of a debriefing form for use in this context is shown in Figure 8.1.

1

About a day ago we needed to take some actions to make things safe for you and other people here.

Do you remember that?

Yes☐

No☐

2

Do you remember what happened

Details:

.....

Yes☐

No☐

3

Do you know the reasons why?

Why?:

.....

Yes☐

No☐

4

Do you believe it was necessary?

Why?:

.....

Yes☐

No☐

5

Do you know what medication was used?

Please specify.

Yes☐

No☐

How did it make you feel (place a circle around the most appropriate number):

Angry

Not angry at all

012345678910

Very angry

Unhappy

Not unhappy at all

012345678910

Very unhappy

Anxious

Not anxious at all

012345678910

Very anxious

Grateful

Not grateful at all

012345678910

Very grateful

Fearful

Not fearful at all

012345678910

Very fearful

Figure 8.1 Example of a 24–48-hour postintervention patient debriefing form.

Managing acute behavioral disturbance: pharmacological strategies

Typical versus atypical antipsychotics

The typical antipsychotics have a long history of use in the management of acute behavioral disturbance in people with psychotic disorders. However, cardiac conduction problems, including the risk of sudden cardiac death (notably with droperidol), has led many clinicians to move away from their use, expressly at high doses. Indeed, droperidol has been removed from hospital formularies in a number of countries. A more prevalent set of problems associated with typical antipsychotics are extrapyramidal side-effects (EPSE) (see Chapter 1). These are of particular concern in the acute setting, with high doses and rapid up-titration often being used. Acute dystonias are very frightening for the patient and laryngeal dystonia can prove fatal; immediate treatment with anticholinergic agents, either intramuscularly (IM) or intravenously (IV), is required. Akathisia is extremely uncomfortable for the patient, and can feed the sense of agitation. Neuroleptic malignant syndrome is a rarer but potentially fatal side-effect, and is again more common in the context of high doses of typical antipsychotics (see Chapter 1). Awareness of these potential outcomes should lead to the monitoring of the patient in terms of mental state, EPSE, and pulse and blood pressure. Serial electrocardiograms and blood tests, including creatine phosphokinase (CPK) levels should be performed where clinically indicated, and whenever high cumulative doses of antipsychotic agents have been administered.

The role of the atypical antipsychotics (e.g. risperidone, aripiprazole, olanzapine, quetiapine, ziprasidone) in the management of acute behavioral disturbance in psychosis has now been supported by two US 'expert consensus' surveys^{14,15}. In clinical trials, oral risperidone has been found to be as effective as, but better tolerated than IM haloperidol when used alone or in combination with lorazepam in the rapid control of acute psychotic agitation¹⁶. Baker et al¹⁷ reported a rapid decrease of agitation in patients with acute psychosis who were treated with rapid initial dose escalation (RIDE) of oral olanzapine (up to 40 mg/day). The availability of liquid or rapidly dispersible forms of these agents has been seen as a bonus in the acute setting. With respect to quetiapine, Arango and Bernado¹⁸, and Ganesan et al¹⁹ suggest that it is effective in reducing aggression and hostility in patients with acute psychosis, especially at doses up to 800 mg/day. Aripiprazole and amisulpride have not to our knowledge been formally evaluated in terms of the immediate acute context, though

they do have the potential benefit of tranquilization without sedation, and lack of cardiac side-effects.

Rapid acting IM formulations of olanzapine and ziprasidone have shown good efficacy and tolerability in several double-blind trials. For example, Wright et al²⁰ compared IM olanzapine with IM haloperidol in the treatment of acute agitation, and demonstrated a faster onset of action with olanzapine, and a lower risk of EPSE²¹. IM ziprasidone also compares favorably with haloperidol in acute behavioral disturbance, and appears to be well tolerated and safe²². Furthermore, IM ziprasidone may be more cost effective than typical antipsychotics in the acute setting, in light of a reduced incidence of acute adverse events that often require extended periods of observation²³. A rapid-acting IM formulation of aripiprazole is currently undergoing trial²⁴. Indicative dosing guidelines for atypical antipsychotics in the acute setting are shown in Table 8.2.

Table 8.2 Dosing guidelines of atypical antipsychotics in treatment of acute arousal		
<i>Formulation</i>	<i>Dosing method</i>	<i>Maximum daily dose</i>
Ziprasidone IM (Pfizer)	10–20 mg increments, 10 mg dose every 2 hours, or 20 mg dose every 4 hours	40 mg
Olanzapine IM (Eli Lilly)	Efficacy for agitation lies within 2.5–10 mg; usual recommended dose is 10 mg; lower dose 2.5–7.5 mg may be considered for elderly, debilitated patients, or patients predisposed to adverse reactions or when clinical factors warrant	Safety has not been established for total daily dose >30 mg
Olanzapine disintegrating tablets (Eli Lilly)	10 mg PO every 2 hours until the occurrence of endpoint of clinical effectiveness or limiting side-effects	40 mg for rapid pharmacological treatment of agitation
Risperidone disintegrating tablets (Janssen)	2 mg PO every 2 hours until the occurrence of endpoint of clinical effectiveness or limiting side-effects	12 mg for rapid pharmacological treatment of agitation

IM, intramuscular.

An algorithmic approach to pharmacological management of acute behavioral disturbance in psychosis

The recent US 'expert consensus' survey¹⁵ regarding the most appropriate goals of emergency interventions and best choice of specific antipsychotic agents, concluded that the atypical antipsychotics are now preferred for the management of agitation in the setting of primary psychotic illnesses. Most clinicians agree that calming the patient without sedation is the most appropriate goal of emergency intervention since it will allow the patient to participate in further assessment and treatment. This, accordingly, is consistent with the Clinical Guidelines on Schizophrenia from the National Institute for Health and Clinical Excellence (NICE) in the UK²⁵.

Rapid tranquilization is aimed for rather than rapid neuroleptization²⁶. Albeit that antipsychotic activity probably begins to accrue within 24 hours of treatment with antipsychotic agents²⁷, full antipsychotic efficacy can take some weeks to be established. High doses or cumulative doses of antipsychotics should be avoided where possible, not least because of the risk of sudden death from cardiac dysrhythmias.

Benzodiazepines may be used alone or as adjunctive medications in certain settings, for example where sedation is required and a relatively non-sedating antipsychotic is being used. There is some evidence that a benzodiazepine used in conjunction with an antipsychotic might have benefit over and above either agent used alone²⁸. Several clinical studies showed a trend towards enhanced symptom reduction, such as agitation/aggression, with combined treatments such as lorazepam plus risperidone²⁹ or oral zuclopenthixol³⁰. Lorazepam is the preferred benzodiazepine, but the intramuscular form is not available in all countries. Clonazepam is a less suitable alternative, having a long half life and being erratically absorbed when administered intramuscularly.

Any pharmacological intervention for acute behavioral disturbance should be tailored to the particular clinical situation and the efficacy monitored closely. Thus, the use of a scale such as that shown in Table 8.1 can guide the intervention and ensure consistency of approach. Figure 8.2 shows an algorithmic approach to the management of acute behavioral disturbance in psychosis, with interventions graded according to the degree of arousal. It should be noted that this algorithm reflects our own particular clinical experience in an Australian context. Other centers have preferences for other medications, and evidence is available to support the use of quetiapine³¹ and ziprasidone³² in these settings.

STEP 1 – (arousal level 2–3) Mildly aroused, pacing, still willing to talk reasonably Moderately aroused, agitated, becoming more vocal, unreasonable, or hostile	STEP 2 – (arousal level 3–4) Moderately aroused, agitated, becoming more vocal, unreasonable, and hostile. Highly aroused, possibly distressed, and fearful.	STEP 3 – (arousal level 4–5) Refusing oral medication, moderately aroused, agitated, becoming more vocal, unreasonable, and hostile. Highly aroused, distressed and fearful; violent toward self, others, or property.
ORAL	ORAL	INTRAMUSCULAR
(Benzodiazepines) lorazepam 1–2.5 mg or diazepam 5–10 mg OR (atypical options) olanzapine 5–10 mg or risperidone 1–2 mg (if less sedation required) Review after 30–60 minutes, repeat if necessary. <i>If still ineffective, consider Step 2</i>	(Atypical options) olanzapine 10–20 mg OR risperidone 2–4 mg PLUS lorazepam 1 mg–2.5 mg or diazepam 5–10 mg OR (typical option: less preferred) chlorpromazine 100–200 mg or haloperidol 5–10 mg Review after 30–60 minutes, repeat if necessary. <i>If still ineffective, consider Step 3</i>	(Atypical option) olanzapine 10 mg OR lorazepam 1–2.5 mg or clonazepam 1–2 mg (if more rapid but shorter effect is required, consider midazolam 0.1 mg/kg) OR (typical option: less preferred) haloperidol 5–10 mg Review after 30 minutes, repeat if necessary. Clopixol acuphase might be used as per separate protocol
Precautions Lower doses should be considered in the elderly, patients with low body weight, dehydration, or no previous exposure to antipsychotic medications. Monitor respiratory function when benzodiazepines are administered parenterally. Monitor postural blood pressure 30 minutes post-dose. Monitor ECG if using high doses of antipsychotics, notably typicals.	Create opportunity and environment for patient to express fears, frustration, anger, anxiety and triggers (Ventilation) Explore with patient what interventions/solutions would assist them to gain control (Redirection) Assess 'time out' opportunity for patient to regain control (5–15 minutes duration) (Time out) If clinical situation warrants, patient may require restraint (Restraint) If required to place client in a safe environment seclusion might be considered. Explanation to be given to patient and staff. Additional PRN may be required (Seclusion)	ALERT EPSE should be monitored and treated Benzotropine 2 mg IM or IV may be required for acute dystonias (max 6 mg/24 hours) Anticholinergic agents NOT to be used routinely but on an as required (PRN) basis. There are concerns regarding concomitant use of intramuscular olanzapine plus a benzodiazepine; thus, a gap of at least 2 hours is recommended between such agents.

Figure 8.2 Guidelines for pharmacological management of acute arousal and agitation in psychosis. These guidelines reflect the author's clinical experience in an Australian context. Options not detailed here, but those which have clinical and research support include ziprasidone and quetiapine (see text). PRN, pro re nata.

These guidelines have been modified and refined with serial clinical audits. Although effective in the vast majority of cases, they are only guidelines and can be modified in particular clinical situations. For example, good response to a particular agent in the past would support its use again, whilst benzodiazepines, which cause respiratory depression, should probably be avoided in patients with severe respiratory problems. Care should be taken with patients who have had an adverse reaction to an agent in the past; a history of neuroleptic malignant syndrome is of particular concern. Finally, it should be noted that the use of intravenous administration is not advocated, largely because of the potential for respiratory depression and arrest or cardiac conduction problems with this route. However, the intravenous route might be justified in certain clinical scenarios such as emergency departments, where strict monitoring is mandated and resuscitation equipment is immediately available³³.

Ideally the patient should be offered oral medication in the first instance³⁴, and consent should be attempted for any intervention. If restraint and forced injection is required, certain criteria need to be met, including that the patient is detained under the local Mental Health Act (a single restraint and forced medication may be permissible under duty of care, but this should be done only under exceptional circumstances). It should be noted that in patients experiencing their first episode of psychosis (i.e. neuroleptic naive), and in the elderly, those with medical conditions, or those with a history of adverse reactions to antipsychotics, doses should be lowered.

The administration of medication in this setting should be closely monitored, and the efficacy or otherwise of particular interventions assessed at set time periods, which should be stipulated by the prescribing doctor (usually 30 minutes for intramuscular medications, and 60 minutes for oral medication). A proforma for the documentation of such information is shown in Figure 8.3. This also allows a rapid appraisal of total medication use over a period of time.

The role of zuclopenthixol (Clopixol Acuphase)

One particular agent has a special place in the management of acute behavioral disturbance in psychosis – zuclopenthixol (Clopixol Acuphase (acuphase))^{35,36}. This agent (not available in some countries) is essentially a short-acting depot, with an effect lasting some 24–48 hours. It is very sedating, and the fact that it is relatively long-lasting means that the requirement

WARD	WEIGHT (kg)	AGE	Patient's NameUnit No Christian Name Address SexBirth DateAge
Total Number of Medication Charts Chart Numbers			

[illegible]

Figure 8.3 Agitation and arousal medication chart. Based on charts used at Fremantle Hospital, Western Australia.

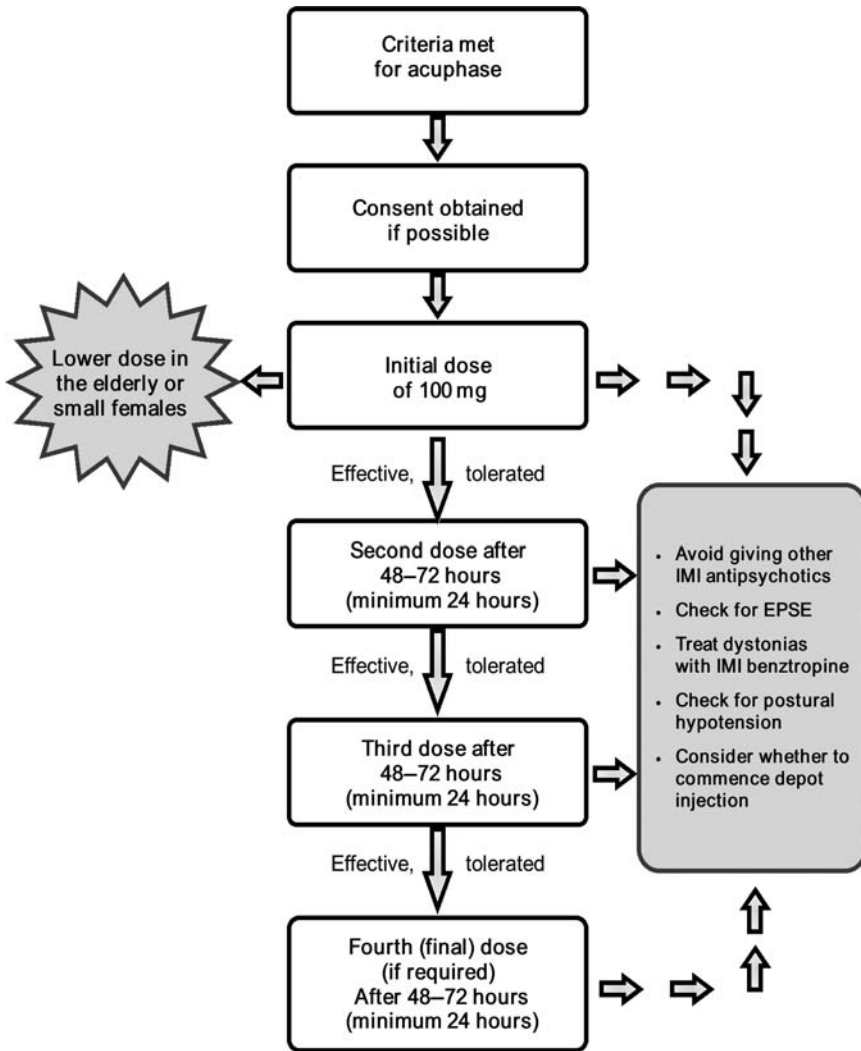


Figure 8.4 Guidelines for the use of zuclopenthixol (Clopixol Acuphase (acuphase)). IMI, intramuscular injection; EPSE, extrapyramidal side-effects. Based of reference 35.

rather than an emergency intervention per se, and an attempt should be made to gain consent from the patient³⁷.

Conclusions

Acute behavioral disturbance is not uncommon in psychiatric settings, potentially endangering both patients and staff. It is important to try to understand

Box 8.3 Guidelines for the use of Clopixol Acuphase (zuclopenthixol acetate)

Initial treatment of **acute arousal and agitation in psychosis** as per Figure 8.2. Acuphase should be considered as a **treatment course** rather than simply a pro re nata (PRN) for acute arousal. An effort should be made, where feasible, to obtain verbal informed consent from the patients. It should not usually be used for first-episode patients.

Suitable patients for the prescription of acuphase

Have required **step 3 injections** as per Figure 8.2 **more than once** and have had **sufficient time for assessment of response and/or side-effects** to previously injected drugs (minimum of 30–60 minutes)

Have previously received Acuphase and have shown a **good tolerability and response** to it

Prescribing information for acuphase:

Usual dose is 100 mg every 48–72 hours

Females, neuroleptic naïve patients and the elderly may require lower doses (25–50 mg)

Large young males may require higher doses (up to 150 mg)

A course of injections would usually be prescribed (e.g. 100 mg every 48–72 hours). Maximum dose is **400 mg over 3 weeks or four injections (whichever comes first)**

A least **24 hours** must elapse between acuphase injections

Review carefully for EPSE and treat rigorously if they occur

Monitor blood pressure carefully (hypotension may occur)

Sedation effects of acuphase

Sedation may initially be seen between **15 and 90 minutes** after injection and **peaks after 8 hours**

Effects last up to 72 hours

The first injection is usually the most sedating

Acuphase may need to be given with IMI lorazepam or midazolam if immediate sedation is required (note: drugs must be given separately and cannot be mixed in the same syringe)

Attempts should be made to avoid the use of **other parenteral antipsychotics** when patients are receiving a course of acuphase

Acuphase may be mixed in the same syringe with the first dose of flupenthixol decanoate or zuclopenthixol decanoate if a depot is to be initiated

Box 8.3 Guidelines for the use of Clopixol Acuphase (zuclopenthixol acetate)—cont'd

Patients in whom caution is advised

Are those concurrently receiving other antipsychotics

Are those sensitive to EPSE

Have pre-existing cardiac disease

TAKE CARE IF PATIENT IS STRUGGLING (dangerous if given accidentally into a vein)

Selection of patients suitable for acuphase

Acuphase is especially effective in the treatment of

aggression/arousal which is difficult to bring under control

relapse of chronic schizophrenia

manic relapse

Adapted from reference 34.

what drives the arousal, and to intervene before matters escalate. Pharmacotherapy with atypical antipsychotics has proven to be an effective strategy in the amelioration of agitation and psychosis in the emergency setting, and mostly is well tolerated. Pharmacological interventions need to be administered in a structured and safe manner, and the effects and side-effects carefully monitored.

Acknowledgments

We wish to acknowledge the staff of the Psychiatric Intensive Care Unit at Fremantle Hospital, Western Australia, and staff at Royal Melbourne, The Austin, and St Vincent's Hospitals in Melbourne, for their role in development and piloting many of the strategies suggested here.

References

1. Meagher DJ. Delirium: the role of psychiatry. *Adv Psychiatr Treat* 2001; 7: 433–43.
2. Meagher DJ. Delirium: optimizing management. *BMJ* 2001; 322: 144–9.
3. Boettger S, Breitbart W. Atypical antipsychotics in the management of delirium: a review of the empirical literature. *Palliat Support Care* 2005; 3: 227–37.
4. Lim CJ, Trevino C, Tampi RR. Can olanzapine cause delirium in the elderly? *Ann Pharmacother* 2006; 40(1): 135–8.

5. Straker DA, Shapiro PA, Muskin PR. Aripiprazole in the treatment of delirium. *Psychomatics* 2006; 47: 385–91.
6. Lee KU, Won WY, Lee HK et al. Amisulpride versus quetiapine for the treatment of delirium: a randomized, open prospective study. *Int Clin Psychopharmacol* 2005; 20(6): 311–14.
7. Castle D, Daniel J, Knott J et al. Development of clinical guidelines for the pharmacological management of behavioural disturbance and aggression in people with psychosis. *Australas Psychiatry* 2005; 13: 247–52.
8. Stevenson S. Heading off violence with verbal de-escalation. *J Psychosoc Nurs Men Health Serv* 1991; 29: 6–10.
9. Brown T. Psychiatric emergencies. *Adv Psychiatr Treat* 1998; 4: 270–6.
10. Kikpatrick H. A descriptive study of seclusion: the unit environment, patient behaviour, and nursing interventions. *Arch Psychiatr Nurs* 1989; 3: 3–9.
11. Wynaden D, Orb A, McGowan S et al. The use of seclusion in the year 2000: What has changed? *Collegian* 2001; 8: 19–25.
12. Smith G, Davis R, Bixler EO et al. Pennsylvania state hospital system's seclusion and restraint reduction program. *Psychiatr Serv* 2005; 56: 1115–22.
13. National Executive Training Institute. Training curriculum for reduction of seclusion and restraint. Alexandria, VA: National Association of State Mental Health Program. Directors, National Technical Assistance Centre for State Mental Health Planning.
14. Allen MH, Currier GW, Hughes DH et al. Treatment of behavioural emergencies. *Postgrad Med* 2001; (Spec No): 1–88.
15. Allen MH, Currier GW, Carpenter D et al. Introduction: methods, commentary, and summary. *J Psychiatr Pract* 2005; 11 (Suppl 1): 5–25.
16. Currier GW, Chou JC, Feifel D et al. Acute treatment of psychotic agitation: a randomized comparison of oral treatment with risperidone and lorazepam versus intramuscular treatment with haloperidol and lorazepam. *J Clin Psychiatry* 2004; 65: 386–94.
17. Baker RW, Kinon BJ, Maguire GA et al. Effectiveness of rapid initial dose escalation of up to forty milligrams per day of oral olanzapine in acute agitation. *J Clin Psychopharmacol* 2003; 23: 342–8.
18. Arango C, Bernado M. The effect of quetiapine on aggression and hostility in patients with schizophrenia. *Hum Psychopharmacol Clin Exp* 2005; 20: 237–41.
19. Ganesan S, Levy M, Bilsker D et al. Effectiveness of quetiapine for the management of aggressive psychosis in the emergency psychiatric setting: a naturalistic uncontrolled trial. *Int J Psychiat Clin Pract* 2005; 9: 199–203.
20. Wright P, Birkett M, David SR et al. Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. *Am J Psychiatry* 2001; 158: 1149–51.
21. Wright P, Lindborg SR, Birkett M et al. Intramuscular olanzapine and intramuscular haloperidol in acute schizophrenia: antipsychotic efficacy and extrapyramidal safety during the first 24 hours of treatment. *Can J Psychiatry* 2003; 48: 716–21.
22. Brook S, Walden J, Beneltia I. Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective: comparison of intramuscular and oral formulation in a 6-week, randomized, blinded assessment study. *Psychopharmacology* 2005; 178: 514–23.
23. Zimbroff DL, Allen MH, Battaglia J et al. Best clinical practice with ziprasidone intramuscular: update after 2 years of experience. *CNS Spectr* 2005; 10 (Suppl 11): 1–15.
24. Modell S, Wilber R, Marcus R et al. Efficacy and safety of intramuscular aripiprazole (abstract). *Eur Psychiatry* 2004; 19 (Suppl 1): 177–8.
25. NICE. Clinical practice algorithms and pathways to care: Schizophrenia – core interventions in the treatment and management of schizophrenia in primary and secondary care. December 2002.

26. Macpherson R, Anstee B, Dix R. Guidelines for the management of acutely disturbed patients. *Adv Psychiatr Treat* 1996; 2: 194–201.
27. Kapur S, Arenovich T, Agid O et al. Evidence for onset of antipsychotic effects within the first 24 hours of treatment. *Am J Psychiatry* 2005; 162: 939–46.
28. Vesper FH, Vesper BD, McMullan JT, Zealberg J, Currier GW. Risperidone versus haloperidol, in combination with lorazepam, in the treatment of acute agitation and psychosis: a pilot, randomized, double-blind, placebo-controlled trial. *J Psychiatr Pract* 2006; 12: 103–8.
29. Lejeune J, Larmo I, Chrzanowski W et al. Oral risperidone plus oral lorazepam versus standard care with intramuscular conventional neuroleptics in the initial phase of treating individuals with acute psychosis. *Intern J Clin Psychopharmacol* 2004; 19: 259–69.
30. Hovens JE, Dries PJ, Melman CT, Wapenaar RJ, Loonen AJ. Oral risperidone with lorazepam versus oral zuclopenthixol with lorazepam in the treatment of acute psychosis in emergency psychiatry: a prospective, comparative, open-label study. *J Psychopharmacol* 2005; 19: 51–7.
31. Pajonk FG, Schwertner AK, Seelig MA. Rapid dose titration of quetiapine for the treatment of acute schizophrenia and acute mania: a case series. *J Psychopharmacol* 2006; 20: 119–24.
32. Preval H, Klotz SG, Southard R et al. Rapid acting IM ziprasidone in a psychiatric emergency service. A naturalistic study. *Gen Hosp Psychiatry* 2005; 27: 140–4.
33. Knott JC, Taylor DM, Castle DJ. Randomised clinical trial comparing intravenous midazolam and droperidol for sedation in the emergency department. *Ann Emerg Med* 2006; 47: 61–7.
34. Currier GW, Medori R. Orally versus intramuscularly administered antipsychotic drugs in psychiatric emergencies. *J Psychiatr Pract* 2006; 12: 30–40.
35. Barnes CW, Alderton D, Castle DJ. The development of clinical guidelines for the use of zuclopenthixol acetate. *Australas Psychiatry* 2002; 10: 54–8.
36. Gibson RC, Fenton M, Coutinho ES, Campbell C. Zuclopenthixol acetate for acute schizophrenia and similar serious mental illness. *Cochrane Database Syst Rev* 2004; (3): CD000525.
37. Fitzgerald P. Long acting antipsychotic medication, restraint and treatment in the management of acute psychosis. *Aust N Z J Psychiatry* 1999; 33: 660–6.

Managing the violent behaviors associated with the schizophrenic syndrome

Paul E Mullen and Danny H Sullivan

There is a statistically and clinically significant correlation between having a schizophrenic syndrome, and increased rates of antisocial behavior in general and violence in particular¹⁻⁷. Studies of homicide offenders consistently indicate that between 5 and 10% will have a schizophrenic disorder (Table 9.1). True rates of schizophrenia among homicide offenders are likely to be at the higher end of these estimates, as nearly all the studies have systematic biases which underestimate the level of the association.

Follow-up studies of large numbers of those with schizophrenia confirm the high levels of violent offending, including killing¹²⁻¹⁴. Up to 10% of homicide offenders may have schizophrenia but the annual risk of a patient with schizophrenia committing a homicide is only in the region of 1 in 10 000, and for acquiring a conviction for violence, 1 in 150¹². Minor forms of assault are more common (5-10% per year) but they are often conceptualized by clinicians not as illness-related but as contextual, 'personality based', or intoxication driven; these attributions may be bolstered by rigid categorical diagnostic systems or forensic formulations required for the legal system. The problems created by the antisocial behavior are further obscured from clinicians because so many who offend are subsequently invisible behind prison walls, where schizophrenia is ten times more common than would be expected by chance¹⁵.

To even begin to manage the propensity to violence associated with having a schizophrenic syndrome, it is necessary to identify what mediates between the condition and the behaviors.

Table 9.1 Studies from a range of countries using different methodologies all suggest that homicide offenders are some ten times more likely to have schizophrenia than would be expected by chance

<i>Authors</i>	<i>Country</i>	<i>Number of homicides</i>	<i>Homicides with schizophrenia</i>	<i>Odds ratio (95% confidence interval)</i>
Hafner and Boker ⁸ (1982)	Western Germany	3367	8.0%	12.7 (11.2–14.3)
Eronen et al ⁹ (1996)	Finland	1037	6.1%	9.7 (7.4–12.6)
Wallace et al ³ (1998)	Victoria, Australia	168	7.2%	10.1 (5.5–18.6)
Erb et al ¹⁰ (2001)	Germany	290 (including attempted)	10.0%	16.1 (11.2–12.5)
Schanda et al ¹¹ (2004)	Austria	1087	5.4%	8.8 (6.7–11.5)

What mediates between the schizophrenic syndrome and violent behavior (Box 9.1 and Figure 9.1)?

Substance abuse

Epidemiological evidence supports a strong association between substance abuse and criminal behavior in those with schizophrenia^{12,16–19}. Correlations and associations do not necessarily reflect causal relationships. A study of 2861 patients first admitted to hospital over a 25-year period with schizophrenia and matched to community controls, demonstrated that although over these years the rate of known substance abuse in patients rose from 8 to 27%, the rate of convictions for violence increased only modestly (from 6 to 10%) in line with the increase among controls (1–3%)¹². This study suggested that over the past 30 years, those with both schizophrenia and a propensity to violence have increasingly turned to substance abuse, rather than violence having increased proportionately with community levels of substance abuse. This interpretation is supported by the work of the groups of both Tengström²⁰ and Veveras¹⁴. Reducing rates of substance abuse in those with schizophrenia is an important therapeutic goal central to improving both symptom control and

Box 9.1 Mediators of violence in schizophrenia.

Substance abuse
 Psychotic symptoms
 Vulnerabilities associated with the illness
 predating onset
 a result of active illness
 related to treatment
 Developmental factors
 Social factors
 Personality factors

quality of life, but although it will almost certainly decrease antisocial behavior, it is unlikely to be a panacea for propensities to violence. The management of substance abuse in people with schizophrenia is covered in more detail in Chapter 7.

Active symptoms

There is a substantial body of clinical experience and literature which supports a connection between active symptoms and antisocial behavior, though

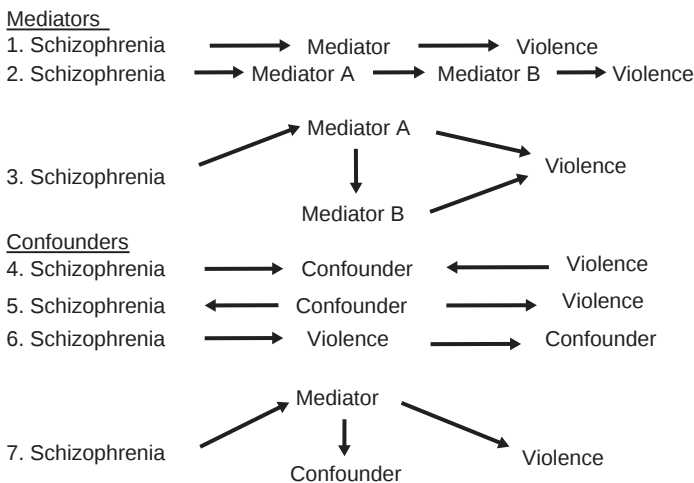


Figure 9.1 Mediators have a causal relationship with schizophrenia and in turn increase the probability of violence and/or are causally related to a third factor which increases the risk of violence (1)–(3). Confounders either have a causal but unrelated relationship with both schizophrenia and violence or are the product of both schizophrenia and violence without mediating any connection between the two (4)–(6). Confounders can also be related to mediators without relating directly to either schizophrenia or violence (7). In practice many factors operate partly as mediators and partly as confounders of the relationship.

not all studies support the role of specific phenomena such as delusions and hallucinations^{5,8 21,22}. Although the role of active symptoms in the violence of schizophrenia has, in our opinion, been overestimated, that they have a role is undoubted. The evidence, for example, of an association between delusional jealousy and attacks on the partner is overwhelming, and persecutory delusions, hallucinations, and non-specific psychotic agitation may all on occasion precipitate violence^{23,24}. However, the purported association between threat-control override symptoms and violence²⁵ is not as clear when different study methodologies are employed²⁶.

There is growing support for a two-type model of violence in schizophrenia^{27,28}. These are shown in Box 9.2. The majority of violence in the schizophrenic population is attributable to type 2, though it is possible that among homicide offenders type 1 is overrepresented. Interestingly, this typology may overlap with the associations which differentiate between antisocial behaviors limited to adolescence and those which persist through the life-course²⁹.

Consequences of the psychopathology of schizophrenia

A number of features of the schizophrenic syndrome are manifest from an early age. Schizophrenia can impact on the risk of violent behavior through:

- Vulnerabilities pre-dating the onset of active symptoms, including developmental difficulties, dissocial traits, educational failure, increased rates of conduct disorder, and early onset substance abuse. The latter is of note as

Box 9.2 The two-type model of violence in schizophrenia.

- Type 1 typically have organized delusional systems which are related to the violence, do not have prominent histories of conduct disorder or adult delinquency, usually commit their first violent offence after entering treatment, almost always attack a carer or acquaintance, and perhaps most importantly are in other senses similar to related patient cohorts
- Type 2 tend to have disorganized clinical syndromes, have histories of conduct disorder and early onset substance abuse, usually a history of multiple violent and non-violent offences prior to diagnosis, commit domestic and non-domestic violence, and are on many measures more similar to offenders than to patients

a common error is to diagnose a drug-induced psychosis in those with schizophrenia whose abuse has preceded their obvious psychotic symptoms.

- Vulnerabilities acquired as a result of active illness, including positive symptoms, personality deterioration, executive dysfunction, social dislocation, substance abuse, incarceration, and unemployment.
- Vulnerabilities related to treatment, such as akathisia and neuroleptic-induced deficit syndrome, and erosion of social skills due to isolation from community life.

Developmental factors

Those with a schizophrenic syndrome at increased risk of violence frequently have histories of developmental problems, poor parenting, and disadvantage during childhood and early adolescence^{30–32}. Histories of conduct disorder in childhood are far more common in this group. So strong is the relationship that it works both ways, with those with histories of conduct disorder having an increased risk of developing schizophrenia later in life³³.

Current social context

Those with schizophrenia often fail to establish work and adult social roles even prior to the recognition of their disorder. Once established, schizophrenia is profoundly associated with unemployment³⁴, which usually brings in its wake financial insecurity and social decline. This tends to encourage a drift into a marginal existence characterized by poor housing, if not homelessness, in socially disorganized neighborhoods where substance abuse, interpersonal conflict, and crime are commonplace. Location of accommodation is associated with violence: the risk of violence in those with major mental disorders was dramatically increased in those discharged from hospital into a high crime neighborhood^{35,36}.

Personality factors

There is now good evidence for personality factors mediating criminality in schizophrenia^{37–40}. Those with the schizophrenic syndrome may become irritable, dissocial, entitled, grandiose, suspicious, and negative; they may be unconcerned (or blind) to the feelings and interests of others, and fail to learn from experience. All factors may be associated with antisocial behavior, including violence. Central to the emergence of violence are both the nature of the person in whom psychosis manifests, and the deleterious effects of the schizophrenic process on their personality.

What is to be done?

The links that mediate between schizophrenia and violence are represented schematically in Figure 9.2. But how can we break these links?

Culture change in generic services

The mental health community has to start by accepting that violent and anti-social behaviors are among the potential complications of having a schizophrenic syndrome. Many services take violent behavior as grounds for exclusion from services. We would argue instead that the research evidence reflects that violent behavior should define increased need for service provision⁴¹ rather than abandonment. With recognition that risk of violence is core business, comes the possibility of remediation. As long as the problem of violence is minimized, sloughed onto other services, or dismissed as ‘not illness related’, there can be no progress in reducing its occurrence or risk. Those at high risk of serious violence, though they constitute less than 10% of those with schizophrenia, need to be prioritized for management. But how can the high risk population be recognized?

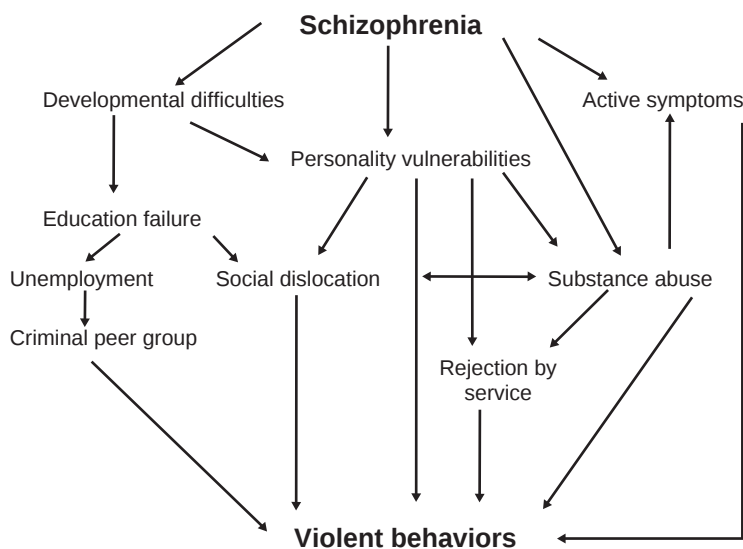


Figure 9.2 The major mediators between having schizophrenia and behaving violently are illustrated. The very complexity of the nexus between illness and violence offers multiple opportunities for intervening to break the links.

Assessment of risk

Many psychiatric services exclude angry young men with substance use problems and forensic issues. Opportunities for early intervention are lost, negative attitudes towards services are engendered in patients, and those of this group at risk of violence either avoid services or are denied them. Risk assessment should commence at the point of triage, when high risk patients may be excluded for spurious reasons or before adequate information exists to determine how best to intervene. Risk assessment is not an arcane art, but a practical guide is provided in Box 9.3.

General principles of management

Many high risk patients will be young, substance abusing, rejecting of treatment, and disorganized. Extended admissions of more than a month are required to enforce a sufficient period of abstinence from cannabis and other

Box 9.3 Risk assessment.

- **Simple** The high risk group will include a large number of young males with a childhood history of conduct disorder, antisocial and violent behavior in adolescence, substance abuse, unemployment, and a disorganized lifestyle
- **Clinical** Risk is dramatically increased in those who are angry and suspicious, lacking insight and rejecting therapy, threatening, and feckless. Specific delusional syndromes, in particular delusional jealousy, dramatically increase risks, as do such personality traits as callousness and entitlement
- **Multidisciplinary** No professional group has a monopoly on the knowledge required to evaluate risk and each should have appropriate input. Current ward behavior, social context, mental state, personality, and intellectual evaluations, and above all a thorough history, are central
- **Systematic** There are many risk assessment instruments of widely varying probity. The best define high risk groups using dynamic as well as static variables, thus allowing recognition of factors to be targeted for intervention. Their prime function for the clinician is to direct attention to known correlates of violent behavior. Instruments can define high risk groups. What they cannot do is tell you with acceptable error rates the chances of any particular individual in that high risk group being violent. This makes them good as tools for needs assessment, and poor as justifications for punitive controls. Instruments like the HCR-20 have a place in structuring the professional's approach to risk assessment, whilst at the same time leaving a place for common sense and clinical knowledge⁴⁹

drugs of abuse to even begin effective treatment of schizophrenic symptoms. Few such patients will be compliant with medications once discharged, nor likely to remain in supervised accommodation of their own accord, but community treatment orders can facilitate compliance, along with other interventions to enhance and monitor compliance with treatment. The responsivity principle⁴¹ requires that high risk patients receive more intensive intervention, such as assertive case management. However, coercion is unlikely to succeed in the long term.

Social interventions

High risk patients on leaving hospital need to be placed in stable accommodation in low crime neighborhoods. This simple and obvious recommendation is rendered hopelessly idealistic by local resistance to locating any accommodation for the mentally ill, let alone mentally abnormal offenders, in more stable neighborhoods. The evidence that marginalization is associated with increased offending has not altered parochial thinking despite strong overall community interests in reducing offending.

In the short term, patients also need regular support from consistent clinicians with whom they have positive relationships, and activities and structure in their lives. In the medium term, programs to enhance social interaction and integration with family when possible, to develop work related skills and provide recreational and sporting activities become the focus. If this population does not acquire a structured and satisfying lifestyle in the long term, be that around vocational activities, recreation or social groups, then they will remain at risk of relapse into substance abuse, downward social drift, and crime. Discharge planning should explicitly factor in goals to ameliorate those social disadvantages which serve as perpetuating factors in violence risk⁴².

Psychological management

Developmental disruptions, genetic predispositions, and the illness process, leave some people with schizophrenia with personality traits and attitudes which might be termed criminogenic. Reducing the possibility of future violence depends to a significant degree on modifying these factors and the behaviors they generate.

Scepticism persists about managing severe personality disorders especially when associated with a schizophrenic syndrome. Partly this reflects the failure of such approaches as dynamic psychotherapies, therapeutic

communities, casework, and simplistic behavior therapies. Personality disorders per se may indeed be untreatable but many of their elements, as found in schizophrenic syndromes, are open to modification and improvement. It is possible to improve interpersonal skills, anger control, assertiveness, victim empathy, and to reduce the cognitive distortions which support violent behaviors^{43,44}. The goal is not the idealistic creation of a benign and prosocial personality, but rather to develop sufficient skills to minimize the deleterious effects of disordered personality on everyday interactions^{45,46}.

Pharmacological management

The primary psychotic illness requires adequate pharmacological treatment (see Chapter 1). Adherence is a key issue in this group (see also Chapter 10) and depot antipsychotic medication is often preferable. Given the need to minimize adverse effects, particularly akathisia and metabolic disturbance, second generation atypical medications are first choice⁴⁷. In terms of depots, currently this restricts the choice to depot risperidone, at least until other atypical depots become available (see Chapter 1). The evidence for antipsychotic medication as having a specific anti-aggressive effect favors clozapine⁴⁸ and in settings where adherence can be monitored or assured, this is the preferable alternative.

Other adjunctive medications may also be used to reduce potential for violence. Benzodiazepines may be useful in the short term, but in the longer term may create potential for conflict in dependent patients seeking escalation of dosage; alprazolam, flunitrazepam, and clonazepam should be used with caution due to an association with increased aggression and behavioral disinhibition. Anti-epileptic drugs may be of benefit, possibly through added sedation, although their toxicity and tolerability limit use, and there are few methodologically rigorous or sustained trials to support their use: carbamazepine, valproate, topiramate and phenytoin have been used. Lithium has demonstrated efficacy in reducing aggression in personality disorder and organic conditions, but may not be tolerated. Serotonergic antidepressants have also undergone trials, but with little evidence of violence reduction except when this is a manifestation of depression.

Substance abuse

The assessment and management of drug and alcohol abuse amongst those with schizophrenia has perforce become a major priority. Substance abuse is

most often present in those at high risk of violence, and its effective control is a prerequisite for any other management. Evaluative debates about the merits of harm minimization as a service-wide philosophy are in our opinion generally secondary to the prevention of violence in populations prone to aggression when intoxicated. This issue is covered fully in Chapter 7.

Restructuring therapeutic goals and service systems

Mental health services, particularly when under pressure, tend to focus on symptom control, which involves a primarily biomedical approach focused on medication. Whether this is ever sufficient is doubtful but in those at high risk of violence it is totally inadequate as all but a holding measure. Substance abuse, personality vulnerabilities, and social context need – if not equal priority with symptom control – at least to be a major part of the management process. If managing the criminogenic and substance abuse issues is to have a chance of success in this group, it has to involve not just adding a few special programs but creating a total immersion for the patient in the drive for change⁷.

Conclusion

The violent behavior associated with the schizophrenic syndrome makes a socially significant contribution to violence in our communities but also lays waste to the lives of those individuals. The 10% or so of those with a schizophrenic syndrome from which will emerge the perpetrators of most of the serious violence are essentially identifiable in advance. A structured program to manage the criminogenic personality and behavioral factors, substance abuse, social dislocation, together with active symptoms could prevent the progress to violence (see Fig 9.3). Such systems of care have the potential to significantly reduce serious criminal violence, including homicide, reduce the number of prisoners with schizophrenia, stop the ever escalating demand for forensic psychiatric beds, and, most important of all, improve the lives of many of the most disturbed and disadvantaged of those with schizophrenia.

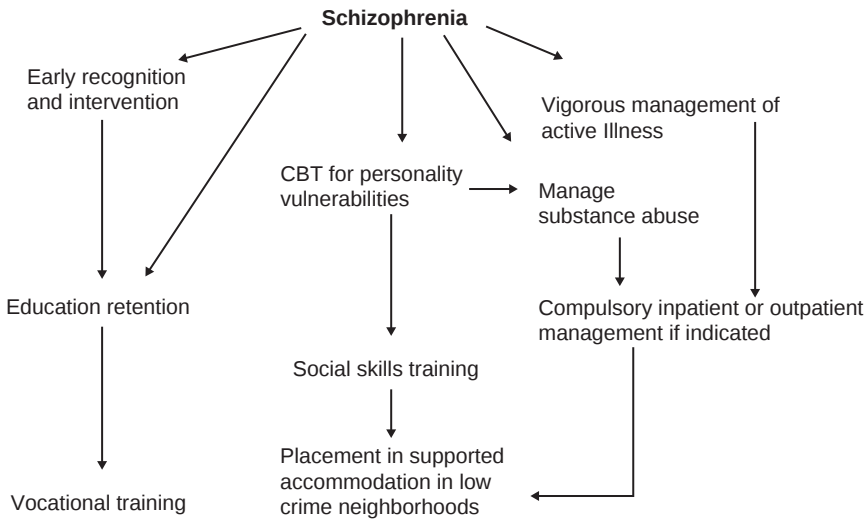


Figure 9.3 *Breaking the links to violent behavior. Some of the interventions which could reduce the strength of the association between having schizophrenia and behaving violently. All interventions depend on accepting that it is the services duty to manage both the violence which can emerge from schizophrenia, and those with schizophrenia who are also substance abusing, delinquent, and objecting. CBT, cognitive behavior therapy.*

References

1. Hodgins S. Mental disorder, intellectual deficiency, and crime – evidence from a birth cohort. *Arch Gen Psychiatry* 1992; 49: 476–83.
2. Hodgins S, Mednick S, Brennan PA et al. Mental disorder and crime: evidence from a Danish birth cohort. *Arch Gen Psychiatry* 1996; 53: 489–96.
3. Wallace C, Mullen PE, Burgess P et al. Serious criminal offending and mental disorder. *Br J Psychiatry* 1998; 172: 477–84.
4. Angermeyer MC. Schizophrenia and violence. *Acta Psychiatr Scand Suppl* 2000; 102: 63–7.
5. Arseneault L, Moffitt T, Caspi A et al. Mental disorders and violence in a total birth cohort: results from the Dunedin Study. *Arch Gen Psychiatry* 2000; 57: 979–86.
6. Walsh E, Buchanan A, Fahy T. Violence and schizophrenia: Examining the evidence. *Br J Psychiatry* 2001; 180: 490–5.
7. Mullen PE. Schizophrenia and violence: from correlations to preventative strategies. *Adv Psychiatr Treat* 2006; 12: 239–48.
8. Hafner H, Boker W. *Crimes of Violence by Mentally Abnormal Offenders*. Cambridge, UK: Cambridge University Press, 1982.
9. Eronen M, Tiihonen J, Hakola P. Schizophrenia and homicidal behavior. *Schizophr Bull* 1996; 22: 83–9.

10. Erb M, Hodgins S, Freese R et al. Homicide and schizophrenia: maybe treatment does have a preventative effect. *Crim Behav Ment Health* 2001; 11: 6–26.
11. Schanda H, Knecht G, Schreinzer D et al. Homicide and major mental disorders: A 25 year study. *Acta Psychiatr Scand* 2004; 110: 98–107.
12. Wallace C, Mullen PE, Burgess P. Criminal offending in schizophrenia over a 25 year period marked by deinstitutionalization and increasing prevalence of comorbid substance use disorders. *Am J Psychiatry* 2004; 161: 716–27.
13. Soyka M, Morhart-Klute V, Schoech H. Neuroscience. Delinquency and criminal offences in former schizophrenic inpatients 7–12 years following discharge. *Eur Arch Psychiatry Clin Neurosci* 2004; 254: 289–94.
14. Vevera J, Hubbard A, Vesely A. Violent behavior in schizophrenia – Retrospective study of four independent samples from Prague, 1949 to 2000. *Br J Psychiatry* 2005; 187: 426–30.
15. Fazel S, Danesh J. Serious mental disorder in 23,000 prisoners: a systematic review of 62 surveys. *Lancet* 2002; 359: 545–50.
16. Swanson JW, Holzer C, Sanju VK et al. Violence and psychiatric disorder in the community: Evidence from the Epidemiological Catchments Area Surveys. *Hosp Community Psychiatry* 1990; 41: 761–70.
17. Steadman HJ, Mulvey EP, Monahan J et al. Violence by people discharged from acute psychiatric inpatient facilities and by others in the same neighborhoods. *Arch Gen Psychiatry* 1998; 55: 393–401.
18. Soyka M. Substance misuse, psychiatric disorder and violent and disturbed behavior. *Br J Psychiatry* 2000; 176: 345–50.
19. Steele J, Darjee R, Thomson LDG. Substance dependence and schizophrenia in patients with violent and criminal propensities. *J Forensic Psychiatry Psychol* 2003; 14: 569–84.
20. Tengström A, Hodgins S, Kullgren G. Men with schizophrenia who behave violently: the usefulness of an early- versus late-start offender typology. *Schizophr Bull* 2001; 27: 205–18.
21. Taylor PJ. Motives for offending among violent and psychotic men. *Br J Psychiatry* 1985; 147: 491–8.
22. Appelbaum PS, Robbins PC, Monahan J. Violence and delusions: data from the MacArthur Violence Risk Assessment Study. *Am J Psychiatry* 2000; 157: 566–72.
23. Mullen PE. Jealousy and the emergence of violent and intimidating behaviors. *Criminal Behav Ment Health* 1996; 6:199–205.
24. Foley SR, Kelly BD, Clarke M et al. Incidence and clinical correlates of aggression and violence at presentation in patients with first episode psychosis. *Schizophr Res* 2005; 72: 161–8.
25. Link BG, Stueve A, Phelan J. Psychotic symptoms and violent behaviors: Probing the components of “threat/control-override” symptoms. *Soc Psychiatry Psychiatr Epidemiol* 1998; 33: S55–60.
26. Stompe T, Ortwein-Swoboda G, Schanda H. Schizophrenia, delusional symptoms, and violence: The threat/control-override concept re-examined. *Schizophr Bull* 2004; 30: 31–44.
27. Steinert T, Voellner A, Faust V. Violence and schizophrenia: Two types of criminal offenders. *Eur J Psychiatry* 1998; 12: 153–65.
28. Ge X, Donnellan MB, Wenk E. Differences in personality and patterns of recidivism between early starters and other serious male offenders. *J Am Acad Psychiatry Law* 2003; 31: 68–77.
29. Moffitt TE, Caspi A. Childhood predictors differentiate life-course persistent and adolescence-limited antisocial pathways among males and females. *Dev Psychopathol* 2001; 13: 355–75.

30. Schanda H, Foldes P, Topitz A et al. Premorbid adjustment of schizophrenic criminal offenders. *Acta Psychiatr Scand* 1992; 86: 121–6.
31. Tiihonen J, Isohanni M, Rasanen P et al. Specific major mental disorders and criminality: A 26-year prospective study of the 1996 Northern Finland Birth Cohort. *Am J Psychiatry* 1997; 154: 840–5.
32. Fresan A, Apiquian R, de la Fuente-Sandoval C et al. Premorbid adjustment and violent behavior in schizophrenic patients. *Schizophr Res* 2004; 69: 143–8.
33. Gosden NP, Kramp P, Gabrielsen G et al. Violence in young criminals predicts schizophrenia: a 9 year register based followup of 15 to 19 year old criminals. *Schizophr Bull* 2005; 31: 759–68.
34. Perkins R, Rinaldi M. Unemployment rates among patients with long-term mental health problems: A decade of rising unemployment. *Psychiatr Bull* 2002; 26: 295–8.
35. Logdberg B, Nilsson L-L, Levander MT. Schizophrenia, neighbourhood, and crime. *Acta Psychiatr Scand* 2004; 110: 92–7.
36. Silver E. Extending social disorganisation theory: a multilevel approach to the study of violence among persons with mental illness. *Criminology* 2000; 38: 1043–74.
37. Nolan KA, Volavka J, Mohr P et al. Psychopathy and violent behavior among patients with schizophrenia or schizoaffective disorder. *Psychiatr Serv* 1999; 50: 787–92.
38. Moran P, Walsh E, Tyrer P et al. Impact of comorbid personality disorder on violence in psychosis. *Br J Psychiatry* 2003; 129: 182–34.
39. Moran P, Hodgins S. The correlates of comorbid antisocial personality disorder in schizophrenia. *Schizophrenia Bulletin* 2004; 30: 791–802.
40. Tengström A, Hodgins S, Grann M et al. Schizophrenia and criminal offending: The role of psychotherapy and substance use disorders. *Criminal Justice Behavior* 2004; 31: 367–91.
41. Andrews DA, Bonta J. *The Psychology of Criminal Conduct*. Cincinnati: Anderson, 1998.
42. Lindqvist P, Skipworth J. Evidence-based rehabilitation in forensic psychiatry. *Br J Psychiatry* 2000; 176: 320–3.
43. Novaco RW. Remediating anger and aggression with violent offenders. *Legal Criminol Psychol* 1997; 2: 77–88.
44. Renwick SJ, Black L, Ramm M. Anger treatment with forensic hospital patients. *Legal Criminol Psychol* 1997; 2: 103–16.
45. McGuire J. *Offender Rehabilitation and Treatment: Effective Programs and Policies to Reduce Re-offending*. Chichester, UK: John Wiley, 2003.
46. Hollin CR. *Handbook of Offender Assessment and Treatment*. Chichester, UK: John Wiley, 2003.
47. Swanson JW, Swartz MS, Elbogen EB. Effectiveness of atypical antipsychotic medications in reducing violent behavior among persons with schizophrenia in community based treatment. *Schizophr Bull* 2004; 30: 3–20.
48. Citrome L, Volavka J, Czobor P et al. Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. *Psychiatr Serv* 2001; 52: 1510–14.
49. Webster CD, Douglas KS, Eaves D et al. *Assessing Risk for Violence*, version 2. British Columbia: Simon Fraser University, 1997.

Understanding and enhancing adherence to treatment in people with schizophrenia

Peter Hayward and Til Wykes

Traditionally, the term ‘compliance’ has been used to refer to the degree to which a patient follows medical advice and complies with treatment recommendations. A patient who takes his medication is said to be ‘compliant’, while one who refuses or forgets is called ‘non-compliant’, or described as showing ‘poor compliance’. It has been suggested that these labels promote a one-sided view of the consultation process: the doctor offers wise and correct advice and the sensible patient obeys without question. The term ‘adherence’ has been advocated recently as suggesting a more active role for the patient, while the Royal Pharmaceutical Society of Great Britain¹ advocates the term ‘concordance’ as promoting the idea of collaboration between patient and prescriber. Ideally, the consultation process and the devising of treatment recommendations, whether they involve pharmacological, psychosocial, or other types of treatment, should be a process of collaborative empiricism where the patient is treated as an equal partner. There is some empirical evidence that this approach leads to superior treatment outcome and greater patient satisfaction; more importantly, this approach respects the autonomy of the patient. How to ensure adherence in practice is what we will expand on throughout this chapter. It should be noted that long acting injectable formulations of antipsychotic agents can play a key role in ensuring adherence in some patients; for details, see Chapter 1.

Factors affecting adherence

A variety of factors can either promote or undermine treatment adherence (see Box 10.1). As a rule, adherence to treatment regimens is far lower for

Box 10.1 Factors affecting adherence.**The Person**

Cultural and family values
 Experiences of illness and treatment
 Support network and milieu
 Personality
 Psychological reactance
 Intelligence
 Views of illness

The Treatment

Therapeutic alliance
 Treatment setting
 Effectiveness
 Complexity
 Side-effects
 Stigma

The Illness

Delusional beliefs
 Positive aspects of illness experience
 Depression/anxiety
 Cognitive impairment
 Lack of motivation

most medical conditions, than professionals might wish. It has been suggested that only around half of patients adhere to a variety of long-term treatment regimens, for illnesses including heart disease, asthma, and AIDS. Consider for a moment the well established rules of a healthy lifestyle: avoidance of alcohol, tobacco, and fattening foods; regular exercise; low levels of stress; daily flossing of the teeth; etc.: do you always adhere to all these practices?

People in general tend to take treatment when they are in distress, while preventative interventions are often forgotten. This is, of course, especially true of patients who don't believe that they are ill, but have other explanations for their problems, such as paranoid or grandiose delusions. Low intelligence quotient (IQ) and disorganized thinking may interfere with adherence, especially if medication regimens are complicated. Side-effects may also be a problem, although a patient may find one particular side-effect intolerable and another much less problematic. One patient might find a certain symptom intolerable and another one mildly annoying, while a second patient reacts in exactly the opposite way. Patients with psychiatric conditions are more likely to adhere to long-term treatments if they see benefit in them, if the treatments are easily available and uncomplicated, and if they are offered in a pleasant and convenient setting by professionals who they like and who show them respect and offer them other kinds of practical help. Most importantly, the treatments should be effective and provide benefits that outweigh their side-effects.

As well as the factors that are outlined in Box 10.1, there are others that affect adherence. These include insight, reactance, and stigma, as described below.

Insight

Traditionally, the term 'insight' is used to mean the correct understanding, by the patient, of his illness. This terminology has been criticized as meaning, in practice, that insight consists of agreeing with the doctor. For many of those with long-term mental illness, their beliefs and experiences seem obviously true, significant, and even in some cases life-enhancing. To perceive oneself as extraordinarily important or in intimate contact with a famous or attractive person might be seen as very desirable, and even to be persecuted by enemies with strange powers might be seen as better than being completely ignored by everyone. While some sufferers may well find the belief that their experiences are 'just an illness' as comforting, others may see it as demeaning, or may well prefer other types of explanations. Some measures of insight actually use treatment adherence as one part of the construct², but it is important to note that having 'good insight' does not necessarily mean that one will adhere to treatment. The opposite can also be true – patients may adhere to a treatment regimen whilst denying the illness for which it was prescribed.

Reactance

The concept of reactance, which has strong theoretical links with that of non-adherence, has been used to describe the tendency for people to react negatively to pressure and coercion. Some people, when told forcibly that they must do something, go along, while others will react in exactly the opposite way; the latter are said to be high in reactance³. Moore et al⁴ found that a scale measuring psychological reactance was a good predictor of treatment adherence. This would suggest that, for those high in reactance, adherence to treatment could best be achieved by a non-confrontational approach, by convincing the patient to choose freely to receive treatment. Unfortunately, many patients undergo their first experience of psychiatric treatment involuntarily, by being detained in hospital. This will often be a highly distressing experience that, whether or not such hospitalization was objectively necessary, will create a legacy of antagonism and resentment in the person detained.

Stigma

There is strong research evidence that lay people hold stigmatizing, prejudiced views about the mentally ill, and that these views discourage sufferers from

seeking treatment⁵. The lay public seems to know relatively little about those with serious mental illness, but to see such people as bizarre, difficult, unhygienic, and dangerous. Further, lay people often define mental illness in terms of treatment received rather than symptoms exhibited. Thus, most people will be slow to accept that they have a stigmatized condition. Labeling in this context becomes very important; we do not have to insist that a person accepts our diagnostic label, or even our label of 'illness', in order for them to benefit from treatment. To say that a treatment 'relieves stress' or 'might help you to cope better' might well be more acceptable to many people, and these statements are also true. If patient and professional agree on a treatment approach, does it really matter if they disagree on a diagnostic label?

Promoting adherence

Failure to adhere to prescribed medication is often said to be one of the major causes of relapse among sufferers from severe mental illness. At the same time, a growing body of research is demonstrating that the principles of cognitive behavioral therapy (CBT) can be used successfully to promote adaptive functioning in a variety of psychiatric conditions including schizophrenia, paranoid psychosis, and other forms of serious mental illness (see Chapter 2). In spite of this, relatively little effort has been made to use CBT techniques to enhance adherence to treatment regimens. Some of the pioneers in the field of CBT for psychosis have suggested the application of such techniques in this area⁶⁻⁸, and a few empirical trials suggest that such approaches can improve adherence and decrease relapse rates⁹⁻¹³. However, this is not a field that has received a lot of empirical investigation, and negative results have also been reported¹⁴. In spite of this, we believe that the CBT approach points the best way to better understanding and concordance between patient and health professional. This is because CBT is, by its very nature, a collaborative enterprise, seeking an agreed model of the difficulties to be addressed and the ways of alleviating those difficulties. In applying such an approach to patients with major mental illness, or, for that matter, any condition requiring medical treatment, the goal should not be to 'get them to take their tablets' but to first create a good treatment alliance, and then to persuade patients to consider various treatment options¹⁵. Whatever the merits of the CBT approach, no one seems to be offering any alternatives. This is unfortunate; by testing alternative approaches, we could learn how to enhance adherence more effectively.

As explained in Kemp et al⁹, the process of building adherence is conceptualized in three stages. The first is to elicit the patient's concerns and problems, and to try to understand his or her model of the root of these difficulties. Initially a review of illness history may be useful, although it goes without saying that it is not helpful to insist that the patient has an illness. Many patients see their problems as external or due to 'stress' or 'pressures of circumstance' rather than as mental illness. Kingdon and Turkington⁶ with their idea of the 'normalizing rationale', are very helpful in this situation: they tell patients that their symptoms are very common, and can be seen in many people under conditions of excessive stress, thus avoiding the stigma that a label of major mental illness carries. The first goal is thus to find a rationale that is acceptable to the patient, so that the idea of medication can be introduced as a possible coping strategy to deal with ongoing problems.

The second key step with any patient is to ask her to consider the advantages and disadvantages of taking medication. Most psychotropic medications have a wide variety of disagreeable side-effects, and other issues, such diagnosis and stigma, may be very important for particular individuals. However, most patients will also be able to pick out advantages in particular medications, ranging from improved sleep to better relationships with loved ones. To avoid reactance, as noted above, the patient must always feel that the final choice is hers. If a patient chooses not to take medication, it is important to maintain a good relationship, so that if she encounters future difficulties, she may be open to reconsidering this decision. The advantage of this approach is that it enhances the therapeutic alliance, which has been shown to be an important predictor of adherence¹⁶.

A useful tool at this point can be some form of self-monitoring¹⁷. A simple form can be developed between the patient and professional, allowing the patient to monitor his mental state and side-effects. A trial period can be suggested, and when it is over, both patient and clinician will have clear evidence as to the effectiveness or otherwise of the particular medication. Formally devised instruments may be less helpful than a simple form that focuses on the patient's own self-chosen problems (see Figure 10.1).

If medication proves effective, and the patient is well, a new problem arises: as noted above, many people find it hard to adhere to regimens of preventative medication, because people are not motivated to take medication when they feel well. This is the third stage of building adherence. The professional

Feeling anxious and threatened				
Much better	A bit better	Same	A bit worse	Much worse
Poor sleep				
Much better	A bit better	Same	A bit worse	Much worse
Restlessness				
Much better	A bit better	Same	A bit worse	Much worse
Ability to concentrate				
Much better	A bit better	Same	A bit worse	Much worse
Feeling that ‘the world depends on me’				
Much better	A bit better	Same	A bit worse	Much worse
Dry mouth				
Much better	A bit better	Same	A bit worse	Much worse
Feeling that ‘The television is talking to me’				
Much better	A bit better	Same	A bit worse	Much worse
Tired/no energy				
Much better	A bit better	Same	A bit worse	Much worse

Figure 10.1 *Personal checklist.*

should offer advice on this point and encourage the use of long-term prophylactic treatment, pointing out both the arguments in favor and the problems many people encounter. However, many patients will probably stop their medication at some point and fall ill again. Such an outcome does not mean that we have failed. The establishment of a good, collaborative relationship should improve long-term engagement with services for most patients. Some patients may not be able to take prophylactic medication at all; for them, short-term medication during acute episodes may be the best option.

We offer a brief summary of some of the key elements in a collaborative approach in Box 10.2. We hope that evidence as to the benefits of this approach will continue to accumulate. In any case, many sufferers, and many professionals, find it to be both helpful and congenial. More research in this neglected field could help to find new ways to foster collaboration between patient and prescriber.

Box 10.2 Enhancing adherence.**Key principles**

Emphasize personal choice and responsibility
 Focus on patient's key concerns, personal goals, and fears and worries
 Express empathy for patient's problems and dilemmas
 Support self-efficacy

Key techniques

Regular summarizing
 Inductive questioning to elicit patient's own concerns
 Explore pros and cons of treatment options
 Use normalizing rationale to combat stigma
 Focus on patient's own long-term goals

Approaches to avoid

Lecturing/preaching
 Insisting on particular diagnostic labels
 Debating with the patient
 Laying down the law

References

1. Royal Pharmaceutical Society of Great Britain. From compliance to concordance: Achieving shared goals in medicine taking. London: RPSGB, 1997.
2. David AS. Insight and psychosis. *Br J Psychiatry* 1990; 156: 798–808.
3. Fogarty JS. Reactance theory and patient noncompliance. *Soc Sci Med* 1997; 45: 1277–88.
4. Moore A, Sellwood W, Stirling J. Compliance and psychological reactance in schizophrenia. *Br J Clin Psychol* 2000; 39: 287–95.
5. Hayward P, Bright JA. Stigma and mental illness: a review and critique. *J Ment Health* 1997; 6: 345–54.
6. Kingdon DG, Turkington D. Cognitive behavioural therapy of schizophrenia. New York: Guilford, 1994.
7. Nelson H. Cognitive behavioural therapy with schizophrenia. Cheltenham: Stanley Thornes, 1997.
8. Beck JS. A cognitive therapy approach to medication compliance. In: Kay J, ed. Integrated Treatment of Psychiatric Disorders. Review of Psychiatry, Washington, D C: American Psychiatric Association, 2001; 20: 113–41.
9. Kemp R, David A, Hayward P. Compliance therapy: an intervention targeting insight and treatment adherence in psychotic patients. *Behav Cogn Psychother* 1996; 24: 331–50.
10. Kemp R, Kirov G, Everitt B et al. Randomised controlled trial of compliance therapy: 18-month follow-up. *Br J Psychiatry* 1998; 172: 413–19.
11. Swanson A, Pantalon MV, Cohen KR. Motivational interviewing and treatment adherence among psychiatric and dually diagnosed patients. *J Nerv Ment Dis* 1999; 187: 630–5.

12. Hayashi N, Yamashina M, Igarashi Y et al. Improvement of patient attitude toward treatment among inpatients with schizophrenia and its related factors: Controlled study of a psychological approach. *Compr Psychiatry* 2001; 42: 240–6.
13. Dolder CR, Lacro JP, Leckband S, Jeste DP. Interventions to improve antipsychotic medication adherence: review of recent literature. *J Clin Pharmacology* 2003; 23: 389–99.
14. O'Donnell C, Donohoe G, Sharkey L et al. Compliance therapy: a randomised controlled trial in schizophrenia. *BMJ* 2003; 327: 1–4.
15. Perkins RE, Repper JM. Compliance or informed choice. *J Ment Health* 1999; 8: 117–29.
16. Day JC, Bentall RP, Roberts C et al. Attitudes towards antipsychotic medication: the impact of clinical variables and relationship with health professionals. *Arch Gen Psychiatry* 1990; 62: 717–24.
17. Randall F, Wood P, Day J et al. Enhancing appropriate adherence with neuroleptic medication: two contrasting approaches. In Morrison AP (Ed.), *A Casebook of Cognitive Therapy for Psychosis*. Hove, UK: Brunner-Routledge, 2002.

Psychological interventions to help people with psychiatric disabilities succeed at work

Morris D Bell and Jimmy Choi

Inactivity and loss of productive function commonly accompany severe psychiatric disorders (such as schizophrenia, other psychotic disorders, mood disorders, and post-traumatic stress disorder (PTSD)). Yet, surveys¹ indicate that more than 75% of people with these disorders wish to return to productive activity of some kind. Vocational services such as supported employment (SE) have helped people with severe and persistent mental illness to obtain community-based competitive jobs by finding appropriate opportunities, often with accommodations and supportive services. SE is now regarded as an evidence-based practice². A manual of SE for serious mental illness (SMI) populations called Individual Placement and Support (IPS) has advanced the implementation of SE. A toolkit is available to assist in implementation¹.

While SE appears superior to other types of vocational services for people with a SMI, employment outcomes remain modest³. Moreover, rates of employment are significantly worse for those people with schizophrenia⁴, which suggests that this group needs interventions that target illness-specific features related to their work impairments. Therefore, SE only partially addresses the problem. It may provide appropriate supports and work opportunity, but patients' work disability remains apparent. People with SMI in SE continue to have difficulty performing their job tasks and often their interpersonal problems disrupt their work. In this chapter, we present psychological interventions to enhance work services, each of which addresses

illness-related deficits that may not be sufficiently overcome through on-the-job supports. These are summarized in Box 11.1.

Work behavior feedback groups with goal setting

Participants receiving work services meet in a weekly group (usually four to eight workers with a facilitator) for approximately 1 hour to review on-site evaluations of members' work performance and to problem-solve and set performance goals for the following week. We have developed these groups in a number of different settings that include transitional and supported employment programs.

To provide systematic feedback, we created the Work Behavior Inventory (WBI) as a standardized work performance assessment instrument⁵. The WBI is rated by a trained vocational counselor who observes workers on the job and interviews their supervisors. The WBI scales are summarized in Box 11.2. For a full discussion of the instrument, see Chapter 17. Research findings indicated that work performance measured by the WBI has a significant relationship to subsequent work outcomes.

In the workers' meetings, half the members receive feedback each week, but all participate in problem-solving and goal setting. The facilitator encourages a process of accurate empathy in which true achievement is acknowledged

Box 11.1 Summary of interventions to augment work programs for people with schizophrenia.

- The first addresses the problem that patients are often poor at judging their own performance and social interactions on the job, making it more difficult for them to improve their work performance or handle interpersonal problems that can lead to job loss. In a weekly group, clients receive accurate feedback about their work performance and set goals for improvement
- The second uses cognitive behavior therapy to address the clients' negative beliefs about themselves as workers and their expectations of failure
- The third method uses psychoeducation and social skills training to teach adaptive responses to many common work problems
- The fourth approach targets underlying cognitive impairments that make it difficult for clients to learn from their experiences on the job. Using cognitive retraining techniques, clients perform computer-based exercises of attention, memory, and problem-solving while they search for and begin working

Box 11.2 Summary of the Work Behavior Inventory.

Work habits
Work quality
Social skills
Cooperativeness
Personal presentation

and praised, and problems are realistically confronted. A good deal of social learning occurs as members help each other and learn from each other's experiences. Each week, members report on their progress toward their individual goals and set new goals, often based on the WBI feedback they have received. Goals might include on-the-job behaviors such as increasing hours of work, being more punctual, being tidier in appearance, taking fewer breaks, or approaching a co-worker about having lunch together. In programs that begin with transitional employment with an expectation of moving on to competitive employment. Goals might also include preparing a resumé, networking for another job, or attending a job interview. There are currently studies underway to determine whether rewards for goal attainment increase vocational outcomes, but results are not yet available.

There are several important reasons for believing that regular work performance feedback and goal setting are especially important for people with severe psychiatric impairment. First, these disorders often impair people's ability to perceive themselves and others accurately. Feedback provides information to workers about their work habits and work quality, and importantly, it evaluates their social skills, personal presentation and cooperativeness on the job. These interpersonal behaviors are crucial for vocational success, yet they are not usually addressed directly by supervisors or co-workers in helpful ways. Left alone, these problems can build up until there is a critical incident leading to job loss. Regular and systematic feedback can provide many people with psychiatric disorders a social prosthesis for their impairments in reading cues from their social environment about their interpersonal behaviors, while goal setting and problem solving can often successfully address these issues. The reader is also referred to Chapter 12 for a fuller discussion on enhancing socialization in people with schizophrenia.

Second, motivation, sense of purpose, and self-confidence can be profoundly affected by psychiatric disorders. Regular feedback provides workers with

a psychiatric disorder continual reassurance about what they are doing right as well as identifying what they need to improve on. Since feelings of worthlessness often lead these workers to believe that others are seeing them as inadequate, getting accurate feedback about how they are viewed by their supervisors can reduce mistrust and provide greater confidence in dealing with people at work. As goals are set and attained, workers develop greater feelings of self-efficacy and become more willing to attempt new challenges.

Finally, research literature from industrial and organizational psychology strongly supports the effectiveness of work feedback and goal setting for improving individual and organizational productivity. A review of the literature⁶ on motivation and their experiments in work feedback and goal setting concluded that 'goal-setting theory is among the most valid and practical theories of employee motivation in organizational psychology.'

We studied this intervention with 63 patients with schizophrenia in a transitional work program who were randomized to receive work performance feedback and goal setting, or usual services. Those receiving feedback showed greater overall improvement in work performance, and particularly on WBI social skills, cooperativeness, and personal presentation. They also worked significantly more hours and weeks during the 6-month transitional work period. Additionally, they showed greater improvements on the intrapsychic dimension of the quality of life scale⁷ (QLS) that reflects increased motivation, sense of purpose, and enjoyment in life.⁸ In subsequent studies that employed cognitive behavior therapy (CBT) or cognitive remediation (see below), we have included the work feedback and goal-setting groups as part of the rehabilitation services. We did so because we feel that other psychological interventions combine easily with feedback and goal-setting groups and that these groups may be necessary to generalize the effects of other interventions.

The Indianapolis Vocational Intervention Program: a cognitive behavioral approach

The Indianapolis Vocational Intervention Program (IVIP) offers participants engaged in work activity a weekly group and individual intervention that target beliefs and behaviors which might interfere in their ability to sustain work (see also Chapter 12). In the IVIP model, groups are generally used to teach participants didactic material. Individual sessions are used to apply these to weekly work experience.

Overall both group and individual sessions of the IVIP are based on the principles of CBT. The group is generally 30–40 minutes and involves three activities:

- teaching the week's didactic material;
- assisting participants to put the didactic material into practice with some type of application exercise;
- giving work feedback to participants.

The IVIP didactic curriculum is organized into four 2-week modules (total of eight sessions). These are presented in order and repeated at least three times during participants' 6-month program. The content of each of these modules is summarized in Table 11.3. During the didactic presentation, the scheduled material is presented both abstractly and applied to participant's actual work experiences using a wide variety of exercises. These include scripted, video-taped and spontaneous role-play; practicing progressive muscle relaxation, and generating in-session thought records.

Work feedback, the last aspect of the intervention section, is derived from the WBI. WBI feedback is given to participants every other week for the first 8 weeks and then monthly. The final section of the group session is the 10–15-minute wrap-up during which the group leader asks participants to summarize what they have learned and/or to identify what made the most impact on them.

The individual counseling component of the IVIP is an opportunity for participants to review and apply didactic materials from groups and to learn to identify and conceptualize concerns using the cognitive behavioral model. Before the therapy session begins, participants rate the strength of their conviction and extent of impact for up to four beliefs that participants and therapists have collaboratively identified. Next, participants report the extent to which they worked on and accomplished a mutually agreed upon between-session assignment and give a brief update of the past work week including any mental health concerns. The therapist also reviews the written practice assignment from the last group session.

The IVIP was created to help people with schizophrenia spectrum disorder learn to identify and monitor their own thoughts and behaviors regarding work, and to give themselves an optimal chance for success. It was developed in response to the observation that due to several factors associated with mental illness including stigma, many with schizophrenia view themselves as having limited competence, relatively low value in the eyes of others in their community, and little chance of success at work. They may believe they have

Table 11.3 Description of Indianapolis Vocational Intervention Program (IVIP) group didactic modules

<i>Module title</i>	<i>Session number and title</i>	<i>Session objectives (examples of concepts and skills to be addressed)</i>
Thinking and work	1. Thinking errors and work	Recognize impact of negative thinking Identify automatic thoughts that impact work
	2. Modifying self-defeating thinking	Modify dysfunctional cognitions using 4 A model* Apply 4 A model to participants' work experiences
Barriers to work	3. Problem solving barriers to work	Identify existing or potential barriers to work Employ steps of problem solving to work barriers
	4. Coping with emotions	Define emotional states that threaten work Learn CBT skills to manage difficult emotions
Workplace relationships	5. Accepting and learning from feedback	Differentiate constructive and destructive criticism Apply steps for responding to feedback at work
	6. Effective self-expression	Learn assertive communication principles Practice giving feedback in work settings effectively
Realistic self-appraisal	7. Thinking about capabilities and limitations	Identify thinking errors compromising self-appraisal Identify strengths, limitations, and necessary accommodations
	8. Managing success	Define failure and success via the cognitive model Modify dysfunctional cognitions regarding work failures

*The 4 A model emphasizes the connections between being 'aware', 'answering', 'acting', and 'accepting'.

little ability to influence their lives and have developed a personal narrative in which failure in social and vocational contexts is expected⁹.

To date one randomized controlled study has examined the impact of the IVIP on work outcomes¹⁰. In this study, 50 participants with schizophrenia or schizoaffective disorder were offered a 6-month job placement and randomized to receive IVIP ($n=25$) or support services ($n=25$). Participants in the IVIP group worked significantly more weeks than those in the support group and had better average work performance on the WBI. Baseline and follow-up scores indicated the IVIP group sustained initial levels of hope and self-esteem through follow-up while the support group experienced declines. Results thus

provide initial evidence that the IVIP can assist participants to persist at work and to sustain their hope and enthusiasm over time. This has also been illustrated by one case report to date¹¹. A randomized controlled trial is currently underway of 100 people with schizophrenia spectrum disorders.

Workplace Fundamentals: a social skills approach

The UCLA Social and Independent Living Skills Program is a manualized social skills training intervention for people with SMI. Similar to other modules in the package, Wallace and Tauber¹² developed the Workplace Fundamental skills module, which focuses on social skills in the workplace that may supplement supported employment. Instruction is provided utilizing the same behavioral teaching techniques shown in Box 11.3. Skills are generally taught in weekly group sessions lasting about 90 minutes with participants finishing the module in 12–24 sessions.

The overall goal of the module is to teach nine specific skills grouped into three skill sets on how to sustain employment.

- *Skill set one* identifies key procedures in the workplace (e.g. break times, paydays). This skill set teaches how to identify and obtain information about investments made by the participant at work, called ‘gives’ (time, tools, relationships, etc.), and rewards they receive when they work, called ‘gets’ (pay, satisfaction, etc.).
- In *skill set two*, participants are taught to ‘be on the alert for problems’ so they can examine their work environment and develop a profile of potential

Box 11.3 Outline of the workplace fundamental skills module.

Introduction to skill sets

Videotape demonstration

Role-playing with clinician and peers

Step by step problem-solving to resolve lack of resources to implement skills
(e.g. money, time)

Problem-solving to resolve disparity between learned skills and unexpected outcomes

Invivo assignments to practice skills outside the group under the trainer's supervision

Homework assignments designed to generalize skills to the workplace

problem areas, called 'sweats' (getting along with co-workers, difficult job task, etc.).

- *Skill set three* is about preventing and solving problems identified in the previous set. Participants are taught how to use a general problem-solving method to prevent and solve work-related problems in areas of mental and physical health, substance abuse, interactions with supervisors and co-workers, work performance, and motivation.

The empirical literature behind the UCLA Social and Independent Living Skills Program is substantial, with the programs translated into over 15 languages by separate independent investigators, adapted to numerous ethnic cultures on every continent, and disseminated all over the world to hospitals, in- and outpatient programs, community centers, and day treatment programs. The Workplace Fundamental module developed by Tauber and Wallace in 1999 is, however, relatively new and investigations are only currently emerging regarding its validation and efficacy. To date, only two empirical studies^{12,13} have reported findings on the module in relation to supported employment and provide only weak support of its efficacy. Nonetheless, the soundness of the basic principles and face validity of the curriculum suggest that further research focused on a sample of clients most vulnerable to social skills problems on the job may find that it has a place in augmenting supported employment.

Neurocognitive Enhancement Therapy: a cognitive remediation approach

Neurocognitive Enhancement Therapy (NET) was developed by our group¹⁴ to directly address impairments in elemental cognitive processes that may interfere with new learning, such as occurs in vocational rehabilitation. The reader is referred to Chapter 4 for a detailed discussion of cognition in schizophrenia. NET is primarily comprised of computer-based training tasks with graduated levels of difficulty that challenge cognitive abilities which are often compromised in mental illness (e.g. attention, memory, and executive function). We have used several sources for the cognitive training exercises, and several other software packages are either available or in development. We have primarily used the Psychological Software Services CogReHab software which was originally developed for people with compromised brain function

and modified by us for use in people with schizophrenia. The second set of exercises was developed by us in conjunction with Scientific Learning Corporation, now Positscience (www.positscience.com). Cognitive training tasks include those targeting simple attention, complex attention, and response inhibition; verbal and visual memory; language mediated cognition; category formation; planning; and strategy.

The approach is to have some exercises that narrowly target specific cognitive processes (e.g. visual reaction time), which may have associations to specific brain areas, and to have other types of exercises that use many integrated brain processes. The curriculum of exercises begins with simpler tasks and builds to more complex ones. Subjects graduate to a more difficult level when they achieve and sustain a prescribed level. Cognitive training occurs in the 'Cog Lab', an attractive learning center with multiple computer work stations. Efforts are made to create an up-beat, reinforcing environment with postings of individual accomplishments, and sometimes small prizes for achieving various levels of success. While little is known about how much training is needed, we encourage participants to practice these exercises every day for 1 hour and believe that at least 40 sessions are probably the minimum necessary to achieve clinical benefit, although it takes more than 100 hours to complete the entire curriculum of exercises.

We have incorporated these cognitive training sessions into a comprehensive rehabilitation program that includes the work performance feedback and goal setting group described previously, with the addition of specific feedback about their cognitive functioning on the job. This feedback is based upon the Vocational Cognitive Rating Scale (VCRS)¹⁵ (see Box 11.4) that is rated along with the WBI. Detailed descriptions of these interventions are available elsewhere^{16,17}.

Box 11.4 Vocational Cognitive Rating Scale (VCRS).

Workers are rated at their job site

16 Items

Predicts work performance and productivity outcomes

Subscales include:

executive function

memory

attention

This intervention was developed to address the common cognitive impairments in schizophrenia and other psychotic disorders, which have been identified as rate-limiting factors in social and occupational domains. Over the past few years, a number of studies have found that specific cognitive deficits predicted work performance and outcomes^{18,19}. Evidence of brain plasticity offers a scientific foundation for cognitive remediation. There are several examples of clinical applications of neuroplasticity outside of psychiatry. These include constraint induced movement therapy (CIMT)²⁰ in post-stroke hemiparesis rehabilitation, auditory discrimination training for people receiving hearing aides²¹, and central auditory processing training for dyslexia²². In schizophrenia and other mental illnesses, the basic mechanisms of overcoming learned non-use and facilitating use-dependent cortical reorganization may have particular application.

Several literature reviews of cognitive remediation have been published²³ (see Chapter 4) and most conclude that the literature favors clinical benefit of one type or another. We have conducted two randomized clinical trials that combine our NET training with work services. The first was performed at the Veterans Affairs (VA) Connecticut Healthcare System and involved 6 months of NET plus work therapy (NET+WT) compared with WT alone ($n=145$). The second was at the Connecticut Mental Health Center and involved a year of active intervention that included NET plus a hybrid vocational program (Voc) of transitional and supported employment (NET+Voc) compared with Voc alone ($n=76$). Participants in both studies were diagnosed with schizophrenia or schizoaffective disorder and were treated in outpatient settings. Details of methods are available elsewhere^{14,17}.

We found that participants receiving NET improved on training tasks and that almost half of those with significant clinical deficits on working memory tasks reached normal levels of performance by the conclusion of training²⁴. We tested the generalization of the training to similar but untrained tasks on neuropsychological testing and found significantly greater improvement for those receiving NET¹⁴. We subsequently found that these improvements endured for 6 months after the end of the active training²⁵. Those receiving NET showed greater improvement in work performance (WBI scores) and cognitive performance on the job (VCRS scores) during the active interventions (unpublished data). Most importantly, work outcomes were better for those receiving NET with their work services. In the VA study, those in NET+WT worked significantly more hours ($p < 0.05$) and earned more money during the 6 months following the intervention¹⁶.

In the Connecticut Mental Health Center (CMHC) study, we found that NET combined with our hybrid vocational program led to significantly more hours ($p < 0.05$) worked during the 12 months after the intervention (transitional and competitive employment combined hours) and significantly higher rates ($p < 0.05$) of competitive employment¹⁶.

Taken together these findings suggest that cognitive retraining can have significant functional benefits when included in a comprehensive rehabilitation program that affords opportunity to acquire practical new learning. We believe that cognitive training improves cognitive processing and thereby makes it possible for participants to gain more from other forms of rehabilitation.

McGurk et al²⁶ have recently published the first small ($n = 44$) effectiveness study combining supported employment with cognitive training. They call their program 'Thinking Skills for Work'. Clients with severe mental illness who had had a previous job failure were randomized to receive supported employment or supported employment augmented with their program. Results were remarkable. Those receiving the cognitive augmentation showed significantly greater improvement on cognitive functioning and on depression and autistic preoccupation scores on the positive and negative syndrome scale (PANSS). Clients receiving cognitive augmentation worked more hours and earned more wages. Most importantly, 69.6% achieved competitive employment as compared with only 4.8% of those receiving supported employment alone ($p = 0.000$).

Conclusions

Those looking for ways to improve the lives of people recovering from persistent and severe mental illness may find excitement and hope in the programs that have been presented in this chapter. Supported employment and other work services offer opportunities for community reintegration through the constructive social roles that working provides. For some, working may lead to reduced symptoms, greater self-esteem, and improved quality of life.

The four interventions that we have described address overlapping but distinct areas of impairment that accompany mental illness and that may be barriers to achieving work success. Each of these approaches has a sound rationale and at least some evidence of efficacy. Most have a manual or a systematic description that make it possible to replicate the methods in other settings.

There is every reason to believe that a comprehensive approach to vocational rehabilitation could combine these interventions to the benefit of the patient.

We are not yet at the point where we can be prescriptive about exactly what methods to apply to which patients, and some of these interventions may be better suited to some settings than to others. Yet, there is sufficient evidence to warrant clinicians and vocational specialists, using their own judgment, to enhance their existing work services with these psychological approaches. It is the hope that these interventions will allow people with mental illness to more speedily and effectively reintegrate into their community so that they may lead more satisfying lives.

Acknowledgment

The authors wish to acknowledge Dr Paul Lysaker's contribution to the section on the Indianapolis Vocational Intervention Program.

References

1. Becker D. Supported Employment Toolkit. Lebanon, NH: Psychiatric Research Center, 2002.
2. Bond GR, Becker DR, Drake RE et al. Implementing supported employment as an evidence-based practice. *Psychiatric Serv* 2002; 52: 313–22.
3. Cook JA, Leff HS, Blyler CR et al. Results of a multisite randomized trial of supported employment interventions for individuals with severe mental illness. *Arch Gen Psychiatry* 2005; 62: 505–12.
4. Razzano LA, Cook JA, Burke-Miller JK et al. Clinical factors associated with employment among people with severe mental illness: Findings from the employment intervention demonstration program. *J Nerv Ment Dis* 2005; 193: 705–13.
5. Bryson G, Bell MD, Greig T, Kaplan E. The work behavior inventory: Prediction of future work success of people with schizophrenia. *Psychiatr Rehabil J* 1999; 23: 113–20.
6. Locke EA, Latham GP. Building a practically useful theory of goal setting and task motivation. A 35-year odyssey. *Am Psychol* 2002; 57: 705–17.
7. Heinrichs DW, Hanlon TE, Carpenter WT Jr. The quality of life scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull* 1984; 10: 388–98.
8. Bell MD, Lysaker P, Bryson G. A behavioral intervention to improve work performance in schizophrenia: Work behavior inventory feedback. *J Vocational Rehab* 2003; 18: 43–50.
9. Lysaker PH, Buck KD. Narrative enrichment in the psychotherapy for persons with schizophrenia: A single case study. *Issues Men Health Nurs* 2006; 27: 233–47.
10. Lysaker PH, Bond G, Davis LW et al. Enhanced cognitive behavioral therapy for vocational rehabilitation in schizophrenia: Effects on hope and work. *J Rehabil Res Dev* 2005; 42: 673–82.
11. Davis LW, Lysaker PH, Lancaster RS et al. The Indianapolis Vocational Intervention Program: a cognitive behavioral approach to addressing rehabilitation issues in schizophrenia. *J Rehab Res Develop* 2005; 42: 35–45.
12. Wallace C J, Tauber R. Supplementing supported employment with workplace skills training. *Psychiatr Serv* 2004; 55: 513–15.

13. Mueser KT, Aalto S, Becker DR et al. The effectiveness of skills training for improving outcomes in supported employment. *Psychiatr Serv* 2005; 56: 1254–60.
14. Bell M, Bryson G, Greig T et al. Neurocognitive enhancement therapy with work therapy: effects on neuropsychological test performance. *Arch Gen Psychiatry* 2001; 58: 763–8.
15. Greig T, Bryson G J, Bell MD. Development of a scale for the assessment of cognitive impairments in vocational rehabilitation: Reliability and predictive validity. *J Vocational Rehab* 2004; 21: 71–81.
16. Bell MD, Bryson GJ, Greig TC et al. Neurocognitive enhancement therapy with work therapy: productivity outcomes at 6- and 12-month follow-ups. *J Rehabil Res Dev* 2005; 42: 829–38.
17. Wexler BE, Bell MD. Cognitive remediation and vocational rehabilitation for schizophrenia. *Schizophr Bull* 2005; 31: 931–41.
18. Bell MD, Bryson G. Work rehabilitation in schizophrenia: does cognitive impairment limit improvement? *Schizophr Bull* 2001; 27: 269–79.
19. McGurk SR, Meltzer HY. The role of cognition in vocational functioning in schizophrenia. *Schizophr Res* 2000; 45: 175–84.
20. Taub E, Morris DM. Constraint-induced movement therapy to enhance recovery after stroke. *Curr Atheroscler Rep* 2001; 3: 279–86.
21. Stecker GC, Bowman GA, Yund W et al. Perceptual training improves syllable identification in new and experienced hearing aid users. *J Rehab Res Develop* 2006; 43: 537–52.
22. Merzenich MM, Jenkins WM, Johnston P et al. Temporal processing deficits of language-learning impaired children ameliorated by training. [see comment]. *Science* 1996; 271: 77–81.
23. Twamley EW, Jeste DV, Bellack AS. A review of cognitive training in schizophrenia. *Schizophr Bull* 2003; 29: 359–82.
24. Bell M, Bryson G, Wexler BE. Cognitive remediation of working memory deficits: durability of training effects in severely impaired and less severely impaired schizophrenia. *Acta Psychiatr Scand* 2003; 108: 101–9.
25. Fiszdon JM, Bryson GJ, Wexler BE et al. Durability of cognitive remediation training in schizophrenia: performance on two memory tasks at 6-month and 12-month follow-up. *Psychiatry Res* 2004; 125: 1–7.
26. McGurk SR, Mueser KT, Pascaris A. Cognitive training and supported employment for persons with severe mental illness: One-year results from a randomized controlled trial. *Schizophr Bull* 2005; 31: 898–909.

Enhancing socialization capacities in people with schizophrenia

Shirley M Glynn and Anna Lui

Schizophrenia often entails difficulties in social and/or occupational functioning. While positive (i.e. hallucinations, delusions) and negative (i.e. amotivation, apathy, asociality, anhedonia) symptoms can certainly be distressing in and of themselves, the deleterious effect they have on both community adjustment and subjective quality of life cannot be overestimated¹⁻⁵. Cognitive impairments (problems in concentration, attention, and memory) in schizophrenia are also highly related to poorer functional outcomes^{6,7} (see Chapter 4).

Individuals with schizophrenia are less likely to be employed⁸ and to marry⁹. They often have difficulty parenting their children¹⁰⁻¹³, may have constrained social networks¹⁴, and are more likely to be homeless than the general population¹⁵. They are also at heightened risk for the development of depression and anxiety^{16,17} (see Chapter 5). While long-term studies of prognosis in schizophrenia are hopeful¹⁸, the illness can cause great dysfunction in diagnosed individuals' lives, especially in their adolescence and young to middle adulthood.

Improving socialization requires adequate interpersonal skills and opportunities to utilize the skills. In this chapter, we first discuss the development of the social skills training movement for schizophrenia and other psychiatric disorders. We then present the efficacy data for these types of interventions, and outline the practical difficulties in generalizing skill use to 'the real world', particularly emphasizing limited opportunities for application. Finally, we describe some new technologies to strengthen socialization skills.

The development of the social skills training movement in schizophrenia

The advent of effective antipsychotic medications in the 1950s brought optimism to the field of schizophrenia treatment^{19,20} (see Chapter 1). However, it subsequently became clear that pharmacological treatment alone did not usually restore individuals with schizophrenia to the level of functioning typically found in their non-ill counterparts²¹. There are likely many reasons for this disparity. Persisting negative symptoms, which are less amenable to the impact of antipsychotic agents^{22,23}, are often reflected in asociality and amotivation, and can impact on social and vocational functioning. Even if medications adequately control positive and negative symptoms, individuals who have been ill during much of their adolescence and early adulthood often have missed critical opportunities to master developmental tasks such as moving from home, meeting a partner, and initiating a career. Decades later, with the lapse of time, the potential atrophy of any skills they did possess, and constrained social and vocational opportunities, it can be very difficult for many individuals to accomplish these goals.

During the 1960s and 1970s, a variety of psychosocial interventions began to be implemented in concert with medications to minimize symptoms and/or improve community adjustment in schizophrenia. One of the best studied of these interventions was social skills training²⁴, which was grounded in behavioral principles originally established in animal laboratories and then extended to humans. Early studies demonstrated that, similar to individuals without psychotic disorders, the behavior of people with psychotic disorders could be shaped using behavioral principles such as extinction, rehearsal, reinforcement, prompting, and shaping²⁵. Mental health professionals began using this knowledge to develop treatment programs, which incorporated learning principles to reduce problematic behaviors and promote pro-social behaviors in those with serious and persisting psychiatric illnesses, including schizophrenia.

Social skills have been classified as shown in Box 12.1²⁶. Traditional social skills training focuses on improving the ability to deliver an intended communication ('sending skills'): most early programs placed relatively less emphasis on helping participants perceive and understand the nuances of others' speech or non-verbal behavior ('receiving' and 'processing' skills), and, if they attempted to accomplish this at all, tended to do so in an unsystematic manner.

Box 12.1 Classification of social skills.

Receiving Accurately perceiving the facial expression, body language, and speech of another

Processing Using systematic logic to understand what is being conveyed while avoiding errors such as jumping to conclusions, or personalizing

Sending capacities Clearly reflecting in speech and behavior the response to the information processed

Social skills training programs are described in detailed in a number of comprehensive texts, including those by Bellack et al²⁷, and Liberman et al²⁸. They typically target non-verbal (eye contact, proximity), para-linguistic (voice tone, speech latency), and linguistic behavior (clear, comprehensible speech), with a goal of helping individuals develop the communication skills necessary to meet instrumental and affiliative goals. These interventions are often offered in a group setting, in order to provide individuals with modeling opportunities, multiple sources of feedback, and opportunities to generalize behaviors. In-session work is augmented with out-of-session assignments to strengthen generalization to non-clinic settings.

Social skills training is now widely used in the treatment of schizophrenia. In addition to standing on its own, elements are often a key component of other interventions. For example, communication skills are an explicit component of a number of other interventions, as shown in Box 12.2.

A comprehensive set of modules, incorporating social skills training to address diverse issues such as work place behavior, medication taking, and dating and intimacy, have been developed as part of the UCLA Social and Independent Living Skills program³⁴. Controlled research has demonstrated

Box 12.2 Treatment programs that incorporate communication skills.

Family psychoeducational programs (e.g. behavioral family therapy^{29,30})

Supported employment (practicing with the consumer how to interact during a job interview³¹)

Illness management and recovery (the facilitator coaching the consumer how to interact effectively with the treatment team³²)

Integrated dual disorder treatment (substance refusal skills³³)

that participants can learn the skills taught in the modules³⁵, irrespective of symptom level, and that they can make gains in social adjustment³⁶.

The efficacy of social skills training in schizophrenia

In considering the efficacy of social skills training in schizophrenia, one must make an informed decision—in what domains would the benefits of social skills training be likely to be observed? This is a more complicated question than it might first appear. Early social skills trials in schizophrenia typically involved single case or small studies and investigated whether the skills could even be learned^{37,38}. Consistent with a behavioral approach, the emphasis was on assessing change in the behavioral domain targeted (that is, if you are teaching someone how to initiate a conversation, you would then measure his/her skill in beginning a conversation). However, with the heightened emphasis on relapse prevention as an important goal in an increasingly de-institutionalized population, researchers also began to investigate whether participation in social skills training programs actually impacted on clinical outcomes²⁴. This work was typically grounded in an application of the stress-vulnerability model of schizophrenia^{39,40}, with the idea being that competent use of social skills would reduce ambient stress, and hence relapse.

A series of meta-analyses conducted on the impact of social skills training in schizophrenia concluded that skills can be learned and maintained in the laboratory, but that generalization to the community rarely occurs spontaneously; it typically must be programmed^{41–44}. Use of the skills in the community probably results in the improved social functioning when individuals have been provided with specific generalization training⁴⁵. However, the data on the relationship between social skills training on relapse or clinical status is less conclusive^{43,46}. Given that these programs do not regularly target changes in symptoms, the limited results are not that surprising and emphasize how critical it is to link interventions with likely domains of impact.

Improving social skills in the community

In considering how socialization can be enhanced in people with serious and persisting psychiatric illnesses, two issues become apparent, namely the

complexity of the task and the availability of new social cognition interventions which may improve outcomes. Both of these will be addressed below.

The complexity of enhancing socialization in schizophrenia

One of the primary challenges in helping people with schizophrenia improve their socialization is the limited opportunities to use skills. Even in the general population, social isolation is a common circumstance due to the decline in civic engagement⁴⁷. The erosion of social networks, according to Putnam, is most recognizable by the dwindling memberships in many civic engagements from parent teacher association meetings to amateur sports clubs. Church attendance, one of the most common associational memberships in the US, has also been declining compared with the early 1990s⁴⁸. The proportion of people living alone in the US has increased from 17% in 1970 to 26% in 2005⁴⁹. People are also working longer hours and workplaces are increasingly competitive⁵⁰. Self-reports of loneliness are common, particularly among the elderly and ethnic minorities^{51,52}, although the availability of the internet may somewhat mitigate this problem⁵³.

In light of the difficulty in making social connection in the general population, it is not surprising that social dysfunction and isolation are particularly common in schizophrenia. Unfortunately, in addition to symptoms, individuals with schizophrenia may confront many practical obstacles to increasing their socialization. Those receiving some kind of disability compensation are usually on very modest budgets, which often do not provide extra income to go to concerts, movies, sports, or other social events. Funds are often limited for hobbies which require any financial outlay. Transportation and/or lack of a car may be a limiting factor.

People living in supervised residential settings may have limited opportunities to interact with others who are not disabled. When there are chances to interact with the general public, individuals with schizophrenia often also confront challenges in participating effectively in the social schema⁵⁴ that dictate many interpersonal interactions. For example, in many initial social interactions, people typically inquire about each others' jobs and families. Disabled individuals who are not in the workforce and/or may have limited contact with kin can have difficulty fielding such questions. During times of symptom exacerbations, even the individual's hygiene and grooming may be compromised. Barriers to socialization for people with schizophrenia are summarized in Box 12.3.

Box 12.3 Barriers to socialization for people with schizophrenia.

- Lack of finances to engage in social activities
- Not living with kin
- Estrangement from family and friends
- Lack of transport to attend social functions
- Social skills deficits
- Stigma
- Psychotic symptoms
- Comorbid symptoms (depression, anxiety)
- Cognitive difficulties
- Side-effects of medication (e.g. sedation)

Unfortunately, the spontaneous and unstructured nature of many social interactions makes transfer of skills learned in the clinic to the environment particularly challenging. Furthermore, the voluntary nature of these interactions typically means that the use of a ‘coach’ or ‘support person’ (akin to the types of interventions used in supported employment programs) to facilitate social engagement is very difficult. The onus is on the person with schizophrenia to create or recognize the opportunities to interact with others and then to use his/her skills competently during these opportunities. This can be a formidable task, particularly for a person with a high level of negative symptoms.

One possibility to circumvent this gap is to assist the person with schizophrenia to develop hobbies or leisure time activities, rather than specific interpersonal connections through increasing environmental support. Here, a support person in the community can play a pivotal role in helping the individual acquire any supplies needed for the activity (e.g. inexpensive yarn for knitting, rentable kayaks), identify opportunities and/or locations to participate in the activity (e.g. nearby knitting shop, local pond), and facilitate connection with these venues. Of course, opportunities for social interaction present themselves during each of these activities, but they are part of the process, rather than the outcome. We have used a community-based support person, in conjunction with formal illness management, independent living, social, and problem-solving skills training from the UCLA modules, to improve overall community adjustment in our test of *in vivo* amplified skills Training (IVAST)⁴⁵ (see Box 12.4) in people with schizophrenia and schizoaffective disorder. Similarly, Tauber et al⁵⁵ found that the addition of indigenous

Box 12.4 Elements of in vivo amplified skills training (IVAST).**Skills taught**

- obtaining information about your medication
- knowing correct administration
- identifying side-effects
- negotiating medication issues with your care provider
- identifying warning signs
- managing warning signs
- coping with persistent symptoms
- avoiding alcohol and street drugs
- social problem solving
- keys to successful living
- developing a daily schedule
- choosing and practicing new social activities

Techniques utilized

- Coaching, prompting, modeling
- Behavioral tailoring for medication administration (if needed)
- Behavioral rehearsal for social interactions and negotiations with health-care providers
- Review of clinic-based homework
- Family meetings with supporters
- Generalization of problem-solving to social and illness management issues encountered in the community
- Visiting local social and leisure locations (libraries, coffee shops, etc.)
- Positive social reinforcement for progress toward social and illness management goals

supporters (residential treatment staff, family, friends) to problem solve generalization difficulties could increase the interpersonal problem-solving skills and community functioning benefits accruing from participation in a comprehensive social and independent living skills program.

Nevertheless, there is much work to be done in the area. One of the disturbing features of the community-based care movement in schizophrenia is that we now have a whole generation of people with the illness who have had few or no hospitalizations and are acutely attuned to the activities and lives of their non-ill cohort group. As they progress in their recoveries, they often look with longing at the (apparent) ease with which their non-ill friends make friends, date, move from home, attend school, and pursue careers. The high

levels of stigma surrounding serious and persisting psychiatric illnesses⁵⁶, and severity of symptoms, can render these tasks very formidable for the person with schizophrenia. Involvement in the peer movement⁵⁷, in which people with serious psychiatric illnesses form supportive social networks and assist each other, may be a useful way to bridge this gap.

Social cognition interventions

Above, we discussed the emphasis in most social skills training programs on improving interpersonal ‘sending’ skills – that is, helping individuals convey what they wish to convey with competent verbal, non-verbal, and paralinguistic behavior. However, to be a competent social being, one also has to correctly perceive the behavior of others (‘receiving’ skills) and then infer accurately their intent and disposition (‘processing’ skills). Individuals with schizophrenia often have profound deficits in social cognition areas. They may be unable to recognize facial expressions accurately⁵⁸, they may commit logical errors in interpreting the behavior of others^{59,60}, and/or they may have limited perspective taking⁶¹; these deficits all reduce their ability to interact effectively with others.

These perceiving and processing deficits are the realm of ‘social cognition’, and there are now a number of studies documenting social cognition deficits in schizophrenia⁶² as well as suggesting methods to remediate these difficulties^{63,64}. These interventions can be targeted at a component skill such as improving facial affect recognition⁶⁵ or they can be more comprehensive and address multiple deficits⁶⁴. These programs typically involve repeated practice, behavioral strategies, and presentation of ambiguous social stimuli to help individuals learn to identify and interpret accurately more subtle social cues (see Box 12.5 for the key elements of Penn et al⁶⁴ social cognition and interaction training). While research in this area is very preliminary, this specialized attention to the subtleties of interpersonal interactions would appear to be a critical component to enhancing socialization in schizophrenia.

Conclusions

Social skills deficits and poor community adjustment are common in schizophrenia. Traditional social skills training programs have provided a platform to increase the interpersonal capacities of individuals with schizophrenia. Nevertheless, the generalization of skills to the community has been problematic. New treatment innovations, focusing on using community

Box 12.5 Elements of social cognition and interaction training.**Phase 1 Emotion training****Goals**

- Provide information about emotions and their relationship to thoughts and situations
- Define basic emotions, including paranoia
- Improve emotion perception and emotional guesses
- Normalize paranoia
- Distinguish between justified and unjustified suspiciousness

Techniques

- Psychoeducation
- Within session and homework assignments requiring clients to identify their feelings (and the feelings of others) in different situations
- Making an 'emotion poster', that links emotions to specific facial expressions
- Use of the 'emotion trainer' and the modified micro-expression task to improve emotion perception
- Imitation of facial expressions
- Video-clips of individuals making social cognitive mistakes while interacting with other people

Phase 2 Figuring out situations**Goals**

- Teach clients not to jump to conclusions
- Improve cognitive flexibility in social situations
- Learn distinction between personal and situational attributions
- Learn how to distinguish 'facts' from 'guesses'

Techniques

- Video-clips of actors/actresses jumping to conclusions and making personal rather than situational attributions
- Brainstorming of causes for social situations/outcomes
- Use of photographs to teach clients how to distinguish facts from guesses
- Playing a modified version of 20 questions to strengthen data gathering and help clients better tolerate ambiguity

Phase 3 Integration: checking it out**Goals**

- Collaboratively (with the group) assess the facts/guesses surrounding events in different members' lives
- Recognize that it is sometimes not possible to make good guesses without getting more information
- Teach effective social skills for checking out guesses

Techniques

- Video-clips of actors/actresses checking out their impressions
- Use the 'check-in' procedure for eliciting personal situations
- Integrate facts/guesses exercise with social skills training

supporters to provide opportunities to practice skills, and targeting interventions to the breadth of deficits resulting from problems in social cognition, are very preliminary but promising nonetheless.

References

1. Norman RM, Malla AK, Cortese L et al. Symptoms and cognition as predictors of community functioning: a prospective analysis. *Am J Psychiatry* 1999; 156: 400–5.
2. Norman RM, Malla AK, McLean T et al. The relationship of symptoms and level of functioning in schizophrenia to general wellbeing and the quality of life scale. *Acta Psychiatr Scand* 2000; 102: 303–9.
3. Racenstein JM, Harrow M, Reed R et al. The relationship between positive symptoms and instrumental work functioning in schizophrenia: a 10-year follow-up study. *Schizophr Res* 2002; 56: 95–103.
4. Robinson DG, Woerner MG, McMeniman M et al. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry* 2004; 161: 473–9.
5. Torgalsboen AK. Full recovery from schizophrenia: the prognostic role of premorbid adjustment, symptoms at first admission, precipitating events and gender. *Psychiatry Res* 1999; 88: 143–52.
6. Brekke JS, Raine A, Ansel M et al. Neuropsychological and psychophysiological correlates of psychosocial functioning in schizophrenia. *Schizophr Bull* 1997; 23: 19–28.
7. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 1996; 153: 321–30.
8. Blyler CR. Understanding the employment rate of people with schizophrenia: Different approaches lead to different implications for policy. In: Lezenweger ME, Hooley JM, eds. *Principles of experimental psychopathology: Essays in honor of Brendan A. Maher* Washington, DC: American Psychological Association 2003; 107–15.
9. Hutchinson G, Bhugra D, Mallett R et al. Fertility and marital rates in first-onset schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* 1999; 34: 617–21.
10. Craig T, Bromet EJ. Parents with psychosis. *Ann Clin Psychiatry* 2004; 16: 35–9.
11. Miller LJ. Sexuality, reproduction, and family planning in women with schizophrenia. *Schizophr Bull* 1997; 23: 623–35.
12. Miller LJ, Finnerty M. Sexuality, pregnancy, and childrearing among women with schizophrenia-spectrum disorders. *Psychiatric Serv* 1996; 4: 502–6.
13. Mullick M, Miller LJ, Jacobsen T. Insight into mental illness and child maltreatment risk among mothers with major psychiatric disorders. *Psychiatric Serv* 2001; 52: 488–92.
14. Randolph ET. Social networks in schizophrenia. In: Mueser KT, Tarrier N, eds. *Handbook in social functioning in schizophrenia*. Boston, MA: Allyn and Bacon 1998: 238–48.
15. Susser E, Struening EL, Conover S. Psychiatric problems in homeless men: Lifetime psychosis, substance use, and current distress in new arrivals at New York City shelters. *Arch Gen Psychiatry* 1989; 46: 845–50.
16. Braga RJ, Mendlowicz MV, Marrocos RP et al. Anxiety disorders in outpatients with schizophrenia: prevalence and impact on the subjective quality of life. *J Psychiatr Res* 2005; 39: 409–14.
17. Siris SG. Depression in schizophrenia: perspective in the era of “Atypical” antipsychotic agents. *Am J Psychiatry* 2000; 157: 1379–89.

18. Harding CM, Brooks GW, Ashikaga T et al. The Vermont longitudinal study of persons with severe mental illness: II. Long-term outcome of subjects who retrospectively met DSM-III criteria for schizophrenia. *Am J Psychiatry* 1987; 144: 727–35.
19. May P. *Treatment of Schizophrenia: A Comparative Study of Five Treatment Methods*. New York: Science House, 1968.
20. May PR, Tuma AH, Dixon WJ et al. Schizophrenia: A follow-up study of the results of five forms of treatment. *Arch Gen Psychiatry* 1991; 38: 776–84.
21. Wallace CJ. Community and interpersonal functioning in the course of schizophrenic disorders. *Schizophr Bull* 1984; 10: 233–57.
22. Kirkpatrick B, Fenton WS, Carpenter WT Jr et al. The NIMH-MATRICES consensus statement on negative symptoms. *Schizophr Bull* 2006; 32: 214–19.
23. Meltzer HY, Alphas L, Green AI et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003; 60: 82–91.
24. Wallace CJ, Liberman RP. Social skills training for patients with schizophrenia: a controlled clinical trial. *Psychiatry Res* 1985; 15: 239–47.
25. Meichenbaum DH. The effects of instructions and reinforcement on thinking and language behavior of schizophrenics. *Behav Res Ther* 1969; 7: 101–14.
26. Donahoe CP, Carter MJ, Bloem WD et al. Assessment of interpersonal problem-solving skills. *Psychiatry* 1990; 53: 329–39.
27. Bellack AS, Mueser KT, Gingerich, S et al. *Social Skills Training for Schizophrenia: A Step-by-Step Guide*. New York: Guilford Press, 2004.
28. Liberman RP, DeRisi WJ, Mueser KT. *Social Skills Training for Psychiatric Patients*. Needham Heights, MA: Allyn & Bacon 1989.
29. Falloon IR, Boyd JL, McGill CW. *Family Care of Schizophrenia: A Problem-solving Approach to the Treatment of Mental Illness*. New York, NY: Guilford Press, 1984.
30. Mueser KT, Glynn SM. *Behavioral family therapy for psychiatric disorders*, 2nd edn. Oakland, CA: New Harbinger Publications, 1999.
31. Becker DR, Drake RE. *A Working Life for People with Severe Mental Illness*. New York: Oxford University Press, 2003.
32. Mueser KT, Corrigan PW, Hilton D et al. Illness management and recovery for severe mental illness: A review of the research. *Psychiatr Serv* 2002; 53: 1272–84.
33. Drake RE, Essock SM, Shaner A et al. Implementing dual diagnosis services for clients with severe mental illness. *Psychiatr Serv* 2001; 52: 469–76.
34. Liberman RP, Wallace CJ, Blackwell G et al. Innovations in skills training for the seriously mentally ill: The UCLA Social and Independent Living Skills modules. *Innovations and Research* 1993; 2: 43–59.
35. Eckman TA, Wirshing WC, Marder SR et al. Technique for training schizophrenic patients in illness self-management: a controlled trial. *Am J Psychiatry* 1992; 149: 1549–55.
36. Marder SR, Wirshing WC, Mintz J et al. Two-year outcome for social skills training and group psychotherapy for outpatients with schizophrenia. *Am J Psychiatry* 1996; 153: 1585–92.
37. Hersen M, Bellack AS. A multiple-baseline analysis of social-skills training in chronic schizophrenics. *J Appl Behav Anal* 1976; 9: 239–45.
38. Matson JL, Zeiss AM, Zeiss RA et al. A comparison of social skills training and contingent attention to improve behavioural deficits of chronic psychiatric patients. *Br J Soc Clin Psychol* 1980; 19: 57–64.
39. Nuechterlein KH, Dawson ME. A heuristic vulnerability/stress model of schizophrenic episodes. *Schizophr Bull* 1984; 10: 300–12.
40. Zubin J, Spring B. Vulnerability: A new view of schizophrenia. *J Abnorm Psychol* 1977; 86: 103–26.

41. Benton MK, Schroeder HE. Social skills training with schizophrenics: A meta-analytic evaluation. *J Consult Clin Psychol* 1990; 58: 741–7.
42. Corrigan PW. Social skills training in adult psychiatric populations: a meta-analysis. *J Behav Ther Exp Psychiatry* 1991; 22: 203–10.
43. Dilk MN, Bond GR. Meta-analytic evaluation of skills training research for individuals with severe mental illness. *J Consult Clin Psychology* 1996; 64: 1337–46.
44. Kopelowicz A, Liberman RP, Zarate R. Recent advances in social skills training for schizophrenia. *Schizophr Bull* 2006; 32: S12–23.
45. Glynn SM, Marder SR, Liberman RP et al. Supplementing clinic-based skills training with manual-based community support sessions: effects on social adjustment of patients with schizophrenia. *Am J Psychiatry* 2002; 159: 829–37.
46. Pilling S, Bebbington P, Kuipers E et al. Psychological treatments in schizophrenia: II. Meta-analyses of randomized controlled trials of social skills training and cognitive remediation. *Psychol Med* 2002; 32: 783–91.
47. Putnam R. *Bowling Alone: The Collapse and Revival of American Community*. New York, NY 2001.
48. Barna, Research & Group *The State of the Church*. Ventura, CA: Issachar Resources, The Barna Group, 2000.
49. US Census Bureau. *Americans Marrying Older, Living Alone More, See Households Shrinking*. In: Census Bureau Report. Washington, DC: US Department of Commerce, 2006: 1.
50. The International Labor Organization. *Key Indicators of the Labour Market*. Geneva: The International Labor Organization, 2003: 857.
51. Heinrich LM, Gullone E. The clinical significance of loneliness: a literature review. *Clin Psychol Rev* 2006; 26: 695–718.
52. Locher JL, Ritchie CS, Roth DL et al. Social isolation, support, and capital and nutritional risk in an older sample: ethnic and gender differences. *Soc Sci Med* 2005; 60: 747–61.
53. Morahan-Martin J, Schumacher P. Loneliness and social uses of the Internet. *Comput Human Behav* 2003; 19: 659–71.
54. Corrigan PW, Wallace CJ, Green MF. Deficits in social schemata in schizophrenia. *Schizophr Res* 192; 8: 129–35.
55. Tauber R, Wallace CJ, Lecomte T. Enlisting indigenous community supporters in skills training programs for persons with severe mental illness. *Psychiatr Serv* 2000; 51: 1428–32.
56. Crisp AH, Gelder MG, Rix S et al. Stigmatization of people with mental illnesses. *Br J Psychiatry* 2000; 177: 4–7.
57. Davidson L, Chinman M, Kloos B et al. Peer support among individuals with severe mental illness: a review of the evidence. *Clin Psychol Sci Pract* 1999; 6: 165–87.
58. Mueser KT, Penn DL, Blanchard JJ et al. Affect recognition in schizophrenia: A synthesis of findings across three studies. *Psychiatry* 1997; 60: 301–8.
59. Bentall RP, Corcoran R, Howard R et al. Persecutory delusions: a review and theoretical integration. *Clin Psychol Rev* 2001; 21: 1143–92.
60. Bentall R P, Swarbrick R. The best laid schemas of paranoid patients: autonomy, sociotropy and need for closure. *Psychol Psychother* 2003; 76: 163–71.
61. Langdon R, Coltheart M, Ward PB. Empathetic perspective-taking is impaired in schizophrenia: evidence from a study of emotion attribution and theory of mind. *Cognit Neuropsychiatry* 2006; 11: 133–55.
62. Couture SM, Penn DL, Roberts DL. The functional significance of social cognition in schizophrenia: a review. *Schizophr Bull* 2006; 32: S44–63.
63. Choi KH, Kwon JH. Social cognition enhancement training for schizophrenia: a preliminary randomized controlled trial. *Community Ment Health J* 2006; 42: 177–87.

64. Penn D, Roberts DL, Munt ED et al. A pilot study of social cognition and interaction training (SCIT) for schizophrenia. *Schizophr Res* 2005; 80: 357–9.
65. Wolwer W, Frommann N, Halfmann S et al. Remediation of impairments in facial affect recognition in schizophrenia: efficacy and specificity of a new training program. *Schizophr Res* 2005; 80: 295–303.

Clinical needs of women with schizophrenia

Paul B Fitzgerald and Mary V Seeman

Men and women, as a rule, differ in terms of their expression of schizophrenia. These differences are found in the areas of premorbid functioning, in the triggers that lead to psychotic episodes, in the clinical manifestation of specific symptoms, and in numerous dimensions of outcome. Studies of the pre-illness phase of schizophrenia show premorbid functioning to be superior in young women relative to young men¹, a female advantage found mainly in the domains of social functioning, cognitive functioning, and school and work achievement.

Largely because of relatively good premorbid functioning and the preservation of affect, young women with schizophrenia may be misdiagnosed and initially treated for personality disorder or mood disorder. Clinicians need to be alert to the potentially relatively 'intact' presentation of young women with schizophrenia. At the same time, the abilities that they bring in the social and work sphere need to be supported and enhanced. Women may look as if they do not require the same rehabilitation efforts as young men with schizophrenia but their skills will deteriorate unless they are harnessed and channeled.

Age at onset

The age at onset differs between the genders, with a later onset in women². Importantly, in respect to treatment, prognosis, and the recent focus on early intervention, young women are generally symptomatic somewhat longer prior to first diagnosis than are young men³ and have a longer prodrome. In particular, after the age of 35, new cases of schizophrenia coming to attention generally are women⁴. This group includes both women who have remained psychotic but hidden for a long period of time and women who have developed their psychosis at a later age.

Consequent clinical need

The appearance of new psychotic illness later in life is relatively rare and the diagnosis can easily be missed because clinicians associate schizophrenia with adolescent onset. Differences in clinical presentation in these later onset women, including the relative absence of thought disorder and negative symptoms, the presence of pre-existing social and occupational skills, and the prominence of affective symptoms may blur and delay diagnosis further. These difficulties with detection often mean that women may not be referred to specialized services and their treatment may, therefore, not be optimal.

Presentations and comorbidities

In addition to the later age of onset, schizophrenia in women presents somewhat differently than in men. Women patients have briefer and fewer hospitalizations and may have, overall, a less severe course of illness^{5,6}. They also have more mood features, fewer negative symptoms, and better preserved social skills. Women initially presenting with what appears to be a non-affective psychosis are more likely than men to be subsequently diagnosed with a mood disorder⁷. Rates and the extent of comorbid substance abuse also differentiate the sexes. In general, greater rates of male substance abuse in schizophrenia reflect the analogous situation in non-schizophrenia populations⁸. With regard to the impact of the illness on cognitive performance, some studies have found sex differences, although the direction and degree have not been consistent across all research. Several studies have reported worse performance in male patients⁹, others have reported worse function in female patients, and others report no differences. It appears likely that gender differences will be function specific and may vary with illness subtype and stage of illness.

Consequent clinical need

Because of the frequent affective component to their illness, women with schizophrenia may respond to mood stabilizers, and, as a result, antipsychotic doses may be able to be kept relatively low. Because they tend to smoke, drink, and use drugs less often than men does not, of course, mean that these subjects should not be addressed and explored.

Cognition

Cognitive performance seems dependent to some degree on estrogen levels¹⁰. A potentially important factor in the clinical presentation of women with

schizophrenia is the fluctuation of symptoms across the menstrual cycle. There is evidence that psychotic symptoms worsen in low estrogen phases of the menstrual cycle¹¹ and that specific cognitive performance is estrogen level related¹⁰; however, there is some evidence that such premenstrual symptom exacerbation may be predominately affective in nature¹².

Consequent clinical need

The effect of estrogen on schizophrenia symptoms raises the possibility of varying the dose of antipsychotic medication during the menstrual cycle. This may allow the overall dose of medication administered to be lower, with possible reductions in side-effects such as tardive dyskinesia.

Hormonal therapies may have a role in the treatment of women with psychosis because estrogen acts to modulate dopamine neurotransmission¹³ as well as exerting effects on serotonin¹⁴, and other neurotransmitter systems. Kulkarni et al¹⁵ treated 11 women with antipsychotic medication plus estradiol and these women experienced a more rapid reduction in their psychotic symptoms when compared with a control group. However, the differences were not sustained by week 8 of the study, indicating that the effect of estrogen was temporary or was mainly a catalyst for antipsychotic efficacy. In a subsequent double-blind placebo controlled study by the same researchers, 100 µg transdermal estradiol was significantly superior to transdermal placebo and 50 µg transdermal estradiol¹⁶ in a group of 36 women treated over 28 days. A similar positive effect was seen over 8 weeks with oral ethinyl estradiol¹⁷, but a study using combined 17β-estradiol and norethisterone acetate failed to help prevent relapse¹⁸. A recent Cochrane review concluded that there is currently insufficient evidence to argue for the routine use of estrogen as an adjunct to antipsychotic therapy¹⁹. However, its use might be supported in certain clinical scenarios, as outlined in Box 13.1. It should be stressed that such an

Box 13.1 Potential clinical uses of estrogen augmentation in schizophrenia.

Where the patient experiences an exacerbation of symptoms that clearly appears to relate to fluctuating hormonal levels through the menstrual cycle
In women with resistant symptoms
During life stages where estrogen levels are low (e.g. menopause)
There may also be a role for estrogen in the treatment of tardive dyskinesia

intervention requires consideration of the overall physical status of the women and the cost-benefit of hormonal treatment administration.

A number of small open studies have demonstrated some benefit of estrogen in the treatment of tardive dyskinesia, although these have been limited²⁰. Indirectly, this potential application is supported by an association between polymorphisms in the estrogen receptor-alpha gene and the occurrence of tardive dyskinesia²¹.

Gender-specific response to antipsychotic treatment

In general, improved treatment responses have been reported for women on antipsychotic medication both in time to remission and in dose required to achieve remission²². This may have to do with pharmacokinetic as well as pharmacodynamic factors. The latter refer to the presence of estrogen at neuronal receptor sites, accelerating and enhancing the antipsychotic effect of drugs. The former refer to sex differences in gastrointestinal absorption, different extents of sequestration into adipose tissue, different rates of distribution in the body, different enzymatic activity, and different liver clearance. A major difference in the kinetics of drug metabolism results from the greater adipose content of female bodies and this difference is especially enhanced with age. As most psychotropic drugs are lipophilic they are sequestered, resulting in a longer duration of action.

Consequent clinical need

Differences in antipsychotic pharmacokinetics have a number of potential clinical implications. First, dosages tested predominately in males may result in increased side-effects or altered patterns of clinical symptom response in women. There is, however, less potential for rebound and withdrawal phenomena after drug discontinuation in women, due to the lipid sequestration. This process also suggests that women have a requirement for longer washout periods when undergoing drug trials. Time of the month, weight fluctuations, activity levels, smoking, alcohol intake, and diet all distinguish male and female subjects and influence drug clearance. There is clearly a need for a greater representation of female subjects in drug trials though this is problematic because of well-founded fears of women subjects becoming pregnant during the trial.

Sex differences in response to psychosocial treatments

There is some evidence that the response to psychosocial interventions differs between men and women. The response to inpatient family intervention, in a well-designed randomized trial, was shown to be superior in women²³, but it has also been shown that illness duration may be an important confounder²⁴. One study indicated that the response to skill training may be worse in women²⁵ but that may depend on which skills are being taught.

It is increasingly recognized that the therapeutic relationships formed by patients with schizophrenia play an important role in the recovery process. Schizophrenia, and in particular negative symptoms, affects the capacity of patients to form and maintain interpersonal relationships that may buffer stressful life experiences. Female patients are better able to form therapeutic relationships but may be more sensitive to frequent alterations in health-care providers, a situation that often occurs in public mental health services.

Consequent clinical need

Treating women with schizophrenia may require more personal involvement on the part of the clinician and more attention paid to the continuity of therapeutic relationships.

Longer-term outcome

Overall, the severity of illness expression is less debilitating in women than men during the first decade following onset, but it worsens in subsequent years and eventually approximates that of men²⁶. The marital rates of men, presumably reflecting the age of onset but also the contrasting roles that men and women assume during courtship, almost always have been shown to be lower than those of women²⁷. Homelessness, suicide and being the victim of homicide are further outcome variables that favor women. Women, however, report more fear of being attacked and hurt so that safety issues on wards and in outpatient programs become important concerns for women²⁸.

Impact of illness on sexuality, pregnancy, and parenting

Studies conducted since the institution of policies favoring community treatment of patients with schizophrenia indicate that the illness does not directly

limit the sexual interest or desire of patients and most patients are sexually active²⁹. Side-effects of antipsychotic medication, including sedation and gynecological effects of raised prolactin, may, however, impact on sexual desire and behavior, as outlined in Box 13.2.

The quality of the sexual lives experienced by women with schizophrenia is significantly impacted by other factors as well. Thus, they experience high rates of sexual abuse, feel pressured to have sex or take part in sex-exchange behavior and to engage in activities that place them at substantial risk for sexually transmitted diseases. These activities include having sex more frequently with homosexual and bisexual partners, and having more lifetime partners. In addition, patients with schizophrenia report poorer levels of knowledge in regards to safe sex behavior and family planning issues³⁰.

Amenorrhea and menstrual cycle disruption are commonly caused by antipsychotics, usually secondary to a rise in prolactin, which may (but not always) prevent ovulation. In addition, studies have reported that women with schizophrenia have lower estrogen levels across the menstrual cycle than controls even when treated with atypical antipsychotics and with no elevation in prolactin levels³¹. Pregnancy can, however, occur in the presence of amenorrhea and may pass unnoticed in schizophrenia patients for several months.

Consequent clinical need

The first trimester is a crucial time for making decisions about the advisability of maintaining the pregnancy and also for anticipating any possible teratogenic impact of drug treatment. Women with psychotic disorders need to be counseled about effective contraception and clinicians should be aware of the possibility of pregnancy. Somatic symptoms such as nausea or breast

Box 13.2 Medication-related negative influences on sexual functioning in women with schizophrenia.

Hyperprolactinemia leading to menstrual irregularities, diminished libido,
impaired sexual functioning
Weight gain and negative impact on body image
Sedation
Nocturnal urinary incontinence
Concern regarding potential negative impact of medication on any offspring

swelling may be prematurely discounted and attributed to the effects of antipsychotics rather than to pregnancy.

When pregnancy is wanted, it should be carefully planned with consideration given to the woman's stage of illness, the extent of her social supports, and the likelihood that she will relapse upon withdrawal of medication. Overall, women with schizophrenia have poorer pregnancy-related outcomes³² (see Box 13.3). These are not necessarily consequent upon exposure to antipsychotic medication during pregnancy, and multiple factors need to be considered, including maternal nutrition, smoking, and poor antenatal health care.

It may be appropriate to withdraw antipsychotic therapy prior to conception, although the evidence for risks associated with antipsychotic medication (other than phenothiazines) remains limited^{33,34}. A low maintenance dose may be appropriate, rather than risk relapse and the possible consequent exposure to higher doses³³. There is a larger volume of drug distribution during pregnancy and more metabolizing enzymes on board (from the placenta) so – theoretically – the expectant mother may actually need higher doses than usual for adequate symptom control. On the other hand, if the antipsychotic prescribed has an active metabolite (risperidone is a case in point), pregnancy delivers more drug to the brain. The other important issue is that the rising levels of estrogen facilitate effects of the antipsychotic drug at the level of neuronal receptors.

Looking after pregnant women with schizophrenia is, thus, complicated. There needs to be active support, parenting education, and family networking. Optimal physical health care is required. Children's services may need to be consulted because some women suffering from schizophrenia either may not be able to look after their babies or will need agency as well as family help.

Box 13.3 Potential adverse outcome for offspring of mothers with schizophrenia.

- Miscarriage
- Premature and/or prolonged labor
- Low birth weight infants
- Fetal death in utero
- Congenital abnormalities

Antipsychotic medication, essential to keep the mother with schizophrenia relatively free of delusional thinking, does often induce sedation and sluggishness. Hypotensive effects may cause dizziness when looking after the baby. Sedation is particularly problematic, because the mother wants to be fully awake for the needs of her infant. She may also feel that not taking medication proves to children's services that she is no longer ill.

Motherhood for women with schizophrenia is often complicated by single status, alienation from family of origin, poverty, and poor general health³⁵. These vulnerable mothers face the challenge of mothering difficult to soothe and possibly developmentally delayed children. Parenting help is a crucial aspect for schizophrenia treatment for women.

Menopause

Menopause is associated with a number of new potential stressors including the death of previously supportive parents, aunts, and uncles, ill health of the patient or spouse, and the departure of children from the home³⁶. In addition, hormones may play an important role in mediating the course of schizophrenia at this age. The severity of schizophrenia levels off in men after their forties. This may be related to the depletion of dopamine receptors with age, a decline that is more precipitous in men than in women. In women the pattern may differ³⁷ possibly related to the gradual diminution of the protective effect of estrogen.

In addition, this is a time that is important for the medical health of women with schizophrenia. Due to the effects of medication side-effects such as weight gain and hyperprolactinemia, there is likely to be a higher incidence of a variety of medical disorders including diabetes, breast cancer, osteoporosis, and cardiovascular disease. Elevated prolactin secondary to medication may contribute to a lowering of bone density and increased risk of atherosclerotic cardiovascular disease.

Consequent clinical need

All women with psychotic disorders should be carefully physically assessed prior to menopause and all factors (including family history and type of medication) considered in the evaluation of interventions such as hormone replacement therapy or anti-bone loss medication. Bone densitometry should be considered and all cardiovascular risk factors assessed carefully. The high rates of smoking and sedentary habits in patients with schizophrenia add to

their risk for both osteoporosis and cardiovascular disease. Women with schizophrenia also access medical services including gynecology less readily than controls, which may result in long-term adverse outcomes³⁸. Anti-smoking programs, nutritional advice, and an accent on exercise are part and parcel of rehabilitation in schizophrenia.

Adverse treatment effects

In general, women experience more adverse antipsychotic side-effects than men (see Box 13.4)³⁹. The vulnerability of women to adverse effects may be due to higher concentrations of free drug reaching target sites, an enhancement of dopamine blockade by estrogen, a longer duration of storage of neuroleptics in adipose tissue, a higher prevalence of immune reactions in women than in men, and a greater risk, in women, of drug–drug interactions because of women’s greater likelihood of comorbid (treated) illness^{40,41}.

Some side-effects of antipsychotics may be of different significance to men and women. As a gross generalization, men are most disturbed by side-effects that interfere with performance, especially sexual performance; women tend to be more disturbed by side-effects which affect appearance, weight gain being especially important⁴².

Extrapyramidal motor side-effects are amongst the more common and disabling side-effects of neuroleptics. Acute dystonia, which was long thought to be more prevalent among men, has been shown, in a first episode fixed-dosed

Box 13.4 Adverse side-effects of antipsychotics to which women are particularly prone.

- Parkinsonism
- Tardive dyskinesia
- Sexual dysfunction
- Gynecomastia and galactorrhea
- Menstrual irregularity
- Osteoporosis
- Cardiovascular effects
- Weight gain
- Metabolic effects

10-week study to occur more readily in women⁴³. As Casey points out, earlier clinical studies did not take into account the fact that young male patients were commonly prescribed higher doses than women, probably because they were perceived as more threatening and their behavior was seen as requiring higher, and more rapid dosing.

Historical studies have suggested that tardive dyskinesia is more common in female than male patients treated with neuroleptics⁴⁴. However, a more recent cohort study found tardive dyskinesia to be more common in elderly men, although its severity may be greater in women in their later years⁴⁵. There is also evidence that the severity and incidence of tardive dyskinesia peaks in men at age 50–70 but continues to increase in women with age⁴⁴. The reasons for this are not fully understood.

Consequent clinical need

Although many interventions have been proposed and are under investigation, there is no clear solution to the problem of medication-related weight gain (see Chapter 6); patients need to be carefully monitored and advised in advance as to the benefits of increased physical activity and appropriate dietary alterations. The capacity of patients, especially those with negative symptoms, to make lifestyle changes, however, may be limited.

Conclusion

In this chapter we have considered a variety of clinically relevant issues for addressing the needs of women with schizophrenia. These women present differently from men, at different ages and with different symptom patterns. Importantly, the outcomes they experience also differ quite significantly and the impact of schizophrenia in female patients is likely to be widely felt amongst children, spouses, and other relatives. The treatments required in female patients also differ in a variety of ways from males. There needs to be an expanded focus in clinical treatment and research on issues pertaining to the sexuality of women with schizophrenia, pregnancy and mothering, complications that emerge with menopause, differential rates of side-effects, and the role of various hormonal therapies. Finally, it is important to note that evidence based upon studies of predominately male subjects may not be completely applicable to outcome in women.

References

1. Meuser K, Yarnold P, Levinson D et al. Prevalence of substance abuse in schizophrenia: demographics and clinical correlates. *Schizophr Bull* 1990; 16: 31–56.
2. Hafner H, Maurer K, Löffler W et al. The influence of age and sex on the early course of schizophrenia. *Br J Psychiatry* 1993; 162: 80–6.
3. Sartorius N, Jablensky A, Shapiro R. Cross-cultural differences in the short-term prognosis of schizophrenia psychosis. *Schizophr Bull* 1978; 4: 102–13.
4. Castle D, Murray R. The epidemiology of late-onset schizophrenia. *Schizophr Bull* 1993; 19: 691–700.
5. Goldstein J. Gender differences in the course of schizophrenia. *Am J Psychiatry* 1988; 145: 684–9.
6. Lewine R. Sex differences in schizophrenia: Timing of subtypes? *Psychol Bull* 1981; 90: 423–44.
7. Chaves AC, Addington J, Seeman M et al. One-year stability of diagnosis in first-episode nonaffective psychosis: influence of sex. *Can J Psychiatry* 2006; 51: 711–14.
8. Anthony J, Helzer J. Syndromes of drug abuse and dependence. In: Robins L, Reiger D, eds. *Psychiatric Disorders in American: The Epidemiologic Catchment Area Study* New York, NY: Free Press 1991: 116–54.
9. Hoff A, Riordan H, DeLisi L. Influence of gender on neuropsychological testing and MRI measures of schizophrenic inpatients. *Schizophr Bull* 1992; 82: 257–72.
10. Hoff AL, Kremen WS, Wieneke MH et al. Association of estrogen levels with neuropsychological performance in women with schizophrenia. *Am J Psychiatry* 2001; 158: 1134–9.
11. Hallonquist J, Seeman M, Lang M et al. Variation in symptom severity over the menstrual cycle of schizophrenics. *Biol Psychiatry* 1993; 33: 207–9.
12. Choi SH, Kang SB, Joe SH. Changes in premenstrual symptoms in women with schizophrenia: a prospective study. *Psychosom Med* 2001; 63: 822–9.
13. Kulkarni J. Women and schizophrenia: a review. *Aust N Z J Psychiatry* 1997; 31: 46–56.
14. Robichaud M, Debonnel G. Estrogen and testosterone modulate the firing activity of dorsal raphe nucleus serotonergic neurones in both male and female rats. *J Neuroendocrinol* 2005; 17: 179–85.
15. Kulkarni J, de Castella A, Smith D et al. A clinical trial of the effects of estrogen in acutely psychotic women. *Schizophr Res* 1996; 20: 247–52.
16. Kulkarni J, Riedel A, de Castella AR et al. Estrogen – a potential treatment for schizophrenia. *Schizophr Res* 2001; 48: 137–44.
17. Akhondzadeh S, Nejatisafa AA, Amini H et al. Adjunctive estrogen treatment in women with chronic schizophrenia: a double-blind, randomized, and placebo-controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; 27: 1007–12.
18. Bergemann N, Mundt C, Parzer P et al. Estrogen as an adjuvant therapy to antipsychotics does not prevent relapse in women suffering from schizophrenia: results of a placebo-controlled double-blind study. *Schizophr Res* 2005; 74: 125–34.
19. Chua WL, de Izquierdo SA, Kulkarni J et al. Estrogen for schizophrenia. *Cochrane Database Syst Rev* 2005; (4): CD004719.
20. Glazer W, Naftolin F, Morgenstern H et al. Estrogen replacement and tardive dyskinesia. *Psychoneuroendocrinology* 1984; 10: 345–50.
21. Lai IC, Liao DL, Bai YM et al. Association study of the estrogen receptor polymorphisms with tardive dyskinesia in schizophrenia. *Neuropsychobiology* 2002; 46: 173–5.
22. Seeman M. Interaction of sex, age and neuroleptic dose. *Compr Psychiatry* 1983; 24: 125–8.

23. Haas G, Glick I, Clarkin J et al. Gender and schizophrenia outcome: A clinical trial of inpatient family intervention. *Schizophr Bull* 1990; 16: 277–92.
24. Glick I, Spencer J, Clarkin J et al. A randomised clinical trial of inpatient family intervention. IV. Follow up results for subjects with schizophrenia. *Schizophr Res* 1990; 3: 187–200.
25. Schaub A, Behrendt B, Brenner H et al. Training schizophrenic patients to manage their symptoms: predictors of treatment response to the German version of the Symptom Management Module. *Schizophr Res* 1998; 31: 121–30.
26. Opjordsmoen S. Long-term clinical outcome of schizophrenia with special reference to gender differences. *Acta Psychiatr Scand* 1991; 83: 307–13.
27. Nimgaonkar V, Ward S, Agarde H et al. Fertility in schizophrenia: results from a contemporary US cohort. *Acta Psychiatr Scand* 1997; 95: 364–9.
28. Seeman MV. Single-sex psychiatric services to protect women. *Medscape Womens Health* 2002; 7: 4.
29. Miller L. Sexuality, reproduction, and family planning in women with schizophrenia. *Schizophr Bull* 1997; 23: 623–35.
30. Miller LJ, Finnerty M. Family planning knowledge, attitudes and practices in women with schizophrenic spectrum disorders. *J Psychosom Obstet Gynaecol* 1998; 19: 210–17.
31. Bergemann N, Mundt C, Parzer PH et al. Plasma concentrations of estradiol in women suffering from schizophrenia treated with conventional versus atypical antipsychotics. *Schizophr Res* 2005; 73: 357–66.
32. Bennedsen BE, Mortensen PB, Olesen AV et al. Obstetric complications in women with schizophrenia. *Schizophr Res* 2001; 47: 167–75.
33. Altshuler L, Cohen L, Szuba M et al. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. *Am J Psychiatry* 1996; 153: 592–606.
34. Patton SW, Misri S, Corral MR et al. Antipsychotic medication during pregnancy and lactation in women with schizophrenia: evaluating the risk. *Can J Psychiatry* 2002; 47: 959–65.
35. Seeman MV. Schizophrenia and motherhood. In: Göpfert M, Webster J, Seeman MV, eds *Parental Psychiatric Disorder: Distressed Parents and their Families* Cambridge, UK: Cambridge University Press, 2004: 161–71.
36. Seeman MV. (2002) Does menopause intensify symptoms in schizophrenia? In: Lewis-Hall F, Williams TS, Panetta JA, Herrera JM (eds). *Psychiatric Illness in Women: Emerging Treatments and Research* pp. 239–248. Washington, D.C.: American Psychiatric Press.
37. Seeman MV. Narratives of twenty to thirty year outcomes in schizophrenia. *Psychiatry* 1998; 61: 249–61.
38. Lindamer LA, Buse DC, Auslander L et al. A comparison of gynecological variables and service use among older women with and without schizophrenia. *Psychiatr Serv* 2003; 54: 902–4.
39. McEvoy JP, Meyer JM, Goff DC et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res* 2005; 80: 19–32.
40. Seeman M. Sex Differences in the Prediction of Neuroleptic Response. In: Gaebel W, Awad A (eds). *Prediction of Neuroleptic Treatment Outcome in Schizophrenia*. Wien: Springer-Verlag, 1994: 51–64.
41. Seeman MV. Gender differences in the prescribing of antipsychotic drugs. *Am J Psychiatry* 2004; 161: 1324–33.
42. Seeman M. Schizophrenic men and women require different treatment programs. *Psychiatr Treat Eval* 1983; 5: 143–8.

43. Casey D. Neuroleptic drug-induced extrapyramidal syndromes and tardive dyskinesia. *Schizophr Res* 1991; 4: 109–20.
44. Yassa R, Jeste D. Gender differences in tardive dyskinesia: A critical review of the literature. *Schizophr Bull* 1992; 18: 701–15.
45. Morgenstern H, Glaser W. Identifying risk factors for tardive dyskinesia among long term outpatients maintained with neuroleptic medication. *Arch Gen Psychiatry* 1993; 50: 723–33.

Family intervention in schizophrenia

Christine Barrowclough and Til Wykes

Families play an essential role in supporting people with long-term mental illness in the community. Over 60% of those with a first episode of a major mental illness return to live with relatives¹, and this would seem to reduce by only 10–20% when those with subsequent admissions are included². However, the carer role is often not an easy one and may be associated with considerable personal costs. In schizophrenia, estimates from different studies suggest that up to two-thirds of family members experience significant stress and subjective burden as a consequence of their caregiver role³. Not only is such stress likely to affect the well-being of the relatives and compromise their long-term ability to support the patient, but it may also have an impact on the course of the illness itself and on outcomes for the patient. Hence one of the most important advances in the treatment of schizophrenia in the past 25 years has been the development of family based intervention programs. The efficacy of this form of treatment is now well established, with many randomized controlled trials having demonstrated the superiority of family intervention over routine care in terms of patient relapse and hospitalization outcomes. This chapter outlines the background to this area of work, summarizes the research findings to date, and draws attention to important areas for future development.

Background to family interventions in schizophrenia

The development of multifactorial models of the processes determining risk and relapse in schizophrenia provided the general rationale for the development

of family interventions (see Clements and Turpin⁴ for a review of the models). These 'stress-vulnerability' models emphasized the contribution of psychological and socioenvironmental stressors to the illness course and thereby opened up the way to psychological interventions. In particular, family interventions found much of their initial impetus in the research on expressed emotion (EE). High EE is assessed on the basis of a critical, hostile, or over involved attitude towards the patient on the part of a relative living in the same household. Early studies^{5,6} found that when patients with schizophrenia were discharged home after being hospitalized for a relapse, their risk of subsequent relapse in the short term was greatly increased if one or more family members was assessed to be 'high EE'. These results have been replicated many times and a meta-analysis of 27 studies⁷ confirmed the elevated risk of relapse for patients in high EE households.

So, within the context of stress vulnerability models, an individual's home may be viewed as an environment capable of influencing the illness for better or worse. If attributes of certain households are responsible for precipitating relapse, then they might be identified and modified with a resulting reduction in relapse rates. Throughout the past two decades a series of studies testing this theory have been reported and are described below.

Family intervention studies

There have been several descriptive reviews of the schizophrenia family intervention studies⁸⁻¹². Typically, the controlled trials recruited families at the point of hospitalization of a relative for an acute episode of schizophrenia and began the family intervention when the patient was discharged back to the home. The intervention period lasted from 6 to 12 months, at the end of which patient relapse rates were compared between patients who received the family intervention as an adjunct to routine care and those who received routine care only. Routine care included the use of prophylactic medication. A series of interventions were developed which differed on some important dimensions including:

- the location of the family sessions (home versus hospital base);
- the number of sessions offered;
- the extent of the patient's involvement;
- the precise content of the sessions;
- the mode of delivery.

Since there was no clear understanding of the mechanisms of patient relapse in the home environment, determining the content involved making assumptions about the kinds of problems associated with high EE families which might contribute to stress. In practice, all the studies assumed that families had inadequate knowledge or misunderstandings regarding the illness and placed an emphasis on educating relatives about schizophrenia as an essential component, to the extent that some reviewers have subsumed all family intervention under the category 'psychoeducation'. The other common area targeted was helping the family members to cope with symptom-related difficulties either by a specific problem solving approach¹³ or through the assessment of individual problems and the application of appropriate cognitive behavioral techniques¹⁴. Despite differences in approaches, Mari and Streiner¹⁵ have provided a useful summary of the common 'ingredients' or 'overall principles' of the treatments.

Modifications to family interventions

Family interventions have been adapted to accommodate different needs and formats.

First episode families

Intervention at an early stage is important given that the onset of psychosis is associated with high levels of stress in relatives¹⁶ and that this is a time when there are many concerns, yet families have less knowledge of psychosis to draw on. It is also an opportune time to engage families who are receptive to information and support^{17,18}.

Substance use and psychosis

Levels of substance use in people with psychosis are high and this 'dual diagnosis' presents many challenges to families (see also Chapter 7). Specialist approaches to helping such families have been described^{19,20}. The approach described by Barrowclough reported good outcomes when used alongside individual work with the patient in a randomized controlled trial²¹.

Group family work

Group interventions for families have the advantage of allowing relatives to share experiences. Family groups were reported to have better outcomes than

individual family work²², although a meta-analysis²³ found group treatments to be less effective.

Results from family intervention studies

A number of meta-analytic reviews of family intervention studies have been published^{15,23–26}. These included 13 studies and confirmed the findings from earlier descriptive accounts, concluding that family intervention as an adjunct to routine care decreases the frequency of relapse and hospitalization; and that these findings hold across the wide age ranges, sex differences, and variability in the length of illness found in the different studies. Moreover, the analysis suggests that these results generalize across care cultures where health systems are very different – trials from the UK, Australia, Europe, the People's Republic of China, and the USA were included. A more recent and inclusive review²⁶ examined 25 studies spanning 20 years (1977–1997) and again this meta-analysis confirmed the superiority of family treated patient relapse rates over control groups, finding an effect size of 0.20, corresponding to a decrease in relapse rate of 20% in patients where families received an intervention. Although this treatment effect may seem relatively low, one must bear in mind that this analysis includes studies where the intervention was extremely brief and with little resemblance to the intensive programs in the original studies. For example, the studies of Falloon et al¹³, Leff et al²⁷, and Tarrier et al²⁸ (see Table 14.1) demonstrated decreased relapse rates for family treated patients of approximately 40%. The absence of treatment fidelity measures in many of these studies makes it difficult to judge quality control within or between studies.

Further comparison analyses within the Pitschel-Walz et al²⁶ review draw attention to some of the wide variations in the content and duration of programs in recent years. Longer-term interventions were more successful than short-term interventions, and more intensive family treatments were superior to a more limited approach (for example, where relatives were offered little more than brief education sessions about schizophrenia). When families were provided with an effective 'dose' in terms of duration and intensity of intervention there is some evidence of the long lasting effects from family treatment. Several studies (see Table 14.1) found a significant difference remaining between the intervention and control groups at 2 years, and the 5- and 8-year follow-up data of Tarrier et al³⁵ demonstrated how durable these effects can be. However, it must be emphasized that all the studies show

Table 14.1 Controlled studies comparing family intervention with standard/alternative treatment for patients with schizophrenia (minimum 6 months intervention)

<i>Study</i>	<i>Treatment conditions</i>	<i>n</i>	<i>Type of family intervention</i>	<i>Duration of treatment</i>	<i>Relapse</i>
Kottgen et al, 1984 ²⁹	(1) FI, high EE; (2) RC, high EE; (3) low EE	49	Psychodynamic groups	Up to 2 years	2 years: FI equal to RC either high or low EE families
Falloon et al, 1982 ¹³ , 1985 ³⁰	(1) Behavioral FI + individual patient treatment; (2) individual patient treatment	36	Home-based behavioral FI	2 years	2 years: behavioral FI superior to individual management
Leff et al, 1982 ²⁷ , 1985 ³¹	(1) FI; (2) routine care	24	Groups + individual sessions	9 months	2 years: FI better than RC
Hogarty et al, 1986 ³² , 1997 ³³	(1) FI; (2) social skills; (3) combined FI + social skills; (4) RC	180	High EE learning from low EE Behavioral FI	Up to 2 years	2 years: FI better than RC or social skills
Tarrier et al, 1988 ²⁸ , 1994 ³⁴	(1) Cognitive-behavioral enactive and symbolic; (2) education only; (3) RC	83	Cognitive behavioral FI (families' choice of home or clinic)	9 months	2 years: FI better than education or RC; education and RC equal
Leff et al, 1990 ³⁵	(1) Multiple-family psychoeducation and support; (2) single family psychoeducation and support	23	Multiple-family groups in the clinic; single family sessions at home	1 year	16 months: conditions equal

Continued

Table 14.1 Controlled studies comparing family intervention with standard/alternative treatment for patients with schizophrenia (minimum 6 months intervention)—cont'd

<i>Study</i>	<i>Treatment conditions</i>	<i>n</i>	<i>Type of family intervention</i>	<i>Duration of treatment</i>	<i>Relapse</i>
Mingyuan et al, 1993 ³⁶	(1) Multiple-family psychoeducation and support; (2) RC	3092	Clinic-based lectures and discussions	1 year	1 year: multiple FI better than RC
Randolph et al, 1994 ³⁷	(1) Behavioral FI; (2) RC	39	Clinic-based behavioral FI	1 year	2 years: behavioral FI better than RC
Xiong et al, 1994 ³⁸	(1) Behavioral FI; (2) RC	63	Clinic-based psycho-education, skills training, medication/symptom management	18 months	18 months: behavioral FI better than RC
Zhang et al, 1994 ³⁹	(1) Multiple and single family; (2) Psycho education and support	78	Multiple-family clinic-based psychoeducation counseling, medication/symptom management	1 year	18 months: family education and support better than RC
Zastowny et al, 1992 ⁴⁰	(1) Behavioral FI; (2) Single-family psychoeducation and support	30	Hospital-based behavioral FI; hospital-based single-family psychoeducational advice	1 year	16 months: conditions equal

Table 14.1 Controlled studies comparing family intervention with standard/alternative treatment for patients with schizophrenia (minimum 6 months intervention)—cont'd

<i>Study</i>	<i>Treatment conditions</i>	<i>n</i>	<i>Type of family intervention</i>	<i>Duration of treatment</i>	<i>Relapse</i>
McFarlane et al, 1995 ²²	(1) Multiple-family psychoeducation and support; (2) single-family psychoeducation and support	172	Multiple-family groups or single-family sessions in the clinic	2 years	2 years: multiple-family conditions better than single-family conditions
Linszen et al, 1996 ⁴¹	(1) Behavioral FI + individual patient treatment; (2) individual patient treatment	76	Hospital and home based behavioral FI	1 year	1 year: conditions equal
Schooler et al, 1997 ⁴²	(1) Intensive behavioral FI; (2) supportive family management	313	Home-based behavioral FI; supportive family management = clinic-based family groups	2 years	2 years: conditions equal

RC, routine care; FI, family intervention; EE, expressed emotion.

that relapses increase with the number of years from termination of the intervention. Thus, overall we can conclude that the efficacy of family interventions for reducing relapse is a robust finding, although the effect size of outcomes has decreased somewhat over the years; this latter finding may, in part, be explained by the increased use of group formats.

One of the criticisms of family intervention studies has been their narrow focus on reductions in patient relapse and hospitalizations. Pitschel-Walz et al²² suggest that there are some indications that family interventions have an impact over a wider range of outcomes. For carers, these include a reduction in carer burden, a change from high to low EE status, and an improved knowledge about schizophrenia. For patients, there is some evidence of better medication adherence (this effect would seem to be independent of the effect of family intervention^{33,44}), improved quality of life, and better social adjustment. Several studies have also demonstrated that these improved outcomes are achieved with reduced costs to society^{39,45,46}.

Pilling et al²³ note that the benefits for family members themselves (such as reduced stress and burden) have received relatively little attention. A recent trial⁴⁷ which focused primarily on improving carer outcomes, did not produce encouraging results. These authors conclude that there is still uncertainty about the most effective interventions for improving well-being in carers of people with psychotic disorders.

Dissemination of family interventions

There have been attempts to disseminate the benefits of family intervention in schizophrenia into routine service delivery. This has been largely through training programs designed to provide clinicians, mainly community psychiatric nurses, with the knowledge and skills required to implement the family work (see Tarrier et al⁴⁸ for a review of dissemination programs). Despite the solid evidence base for the efficacy of family based psychological treatment programs in schizophrenia, and the efforts of the training programs, the implementation of family work in routine mental health services has been at best patchy. The consensus view in the literature is that the implementation of family interventions faces complex organizational and attitudinal difficulties⁴⁹⁻⁵¹, and insufficient attention has been paid to these in dissemination programs. In discussing the factors which might make the transference from research to practice difficult, Mari and Streiner¹⁵ suggested

that the requirements of durable service oriented interventions differ from those based on time-limited research models. The need for changing the clinical practice of the whole service rather than training individuals is underlined in the work of Corrigan et al⁵²⁻⁵⁴. However, difficulties arise not only from staff but also from carer reluctance to engage in family work. Several studies^{55,56} of community samples have shown that carer participation in family intervention is relatively low, with only 50% or so of carers taking up the offer of either a support service or family intervention⁵⁶, with possibly higher rates when help is offered at a time of crisis⁴⁶. Alternatives to professionally led interventions have been suggested⁵⁷ such as the psycho-education groups led by carers⁵⁸.

Summary and future directions

In summary, a number of important conclusions can be drawn concerning family intervention studies. First, while there is robust evidence for the efficacy of family interventions in schizophrenia, it is also clear that short education or counseling programs do not affect relapse rates: 'a few lessons on schizophrenia was simply not sufficient to substantially influence the relapse rate'²⁶.

Second, the quality of interventions needs to be enhanced and monitored to ensure that families are offered the intensity of help likely to give them substantial benefits. Successful family interventions require considerable investment in time, skill, and commitment; and since for many patients the effect is to delay rather than to prevent relapse, many patients and families will need long-term and continuing intervention. Work with relatives of recently diagnosed schizophrenia patients indicates that this help needs to begin from the first onset of the psychosis⁵⁹.

Third, although family interventions improve patient outcomes, there has been little progress in how to improve the well-being of carers. If these data were available then it may be possible to increase engagement of family members as otherwise it may significantly impede the progress of the intervention.

Finally, dissemination and engagement issues need to continue to be addressed and new ways found to assist more families. Although many patients and families benefit greatly from the intervention programs, a substantial number of families are hard to engage, and the implementation of family programs within services presents many challenges.

References

1. Macmillan JF, Gold A, Crow TJ et al. The Northwick Park Study of first episodes of schizophrenia: IV Expressed emotion and relapse. *Br J Psychiatry* 1986; 148: 133–43.
2. Gibbons JS, Horn SH, Powell JM et al. Schizophrenia patients and their families. A survey in a psychiatric service based on a district general hospital. *Brit J Psychiatry* 1984; 144: 70–7.
3. Barrowclough C, Tarrier N, Johnston M. Distress, expressed emotion and attributions in relatives of schizophrenic patients. *Schizophr Bull* 1996; 22: 691–701.
4. Clements K, Turpin G. *Innovations in the Psychological Management of Schizophrenia*. Chichester: John Wiley & Sons, UK 1992.
5. Brown GW, Birley JLT, Wing JK. Influences of family life on the course of schizophrenic disorders: a replication. *Brit J Psychiatry* 1972; 121: 241–8.
6. Vaughn C, Leff J. The influence of family and social factors on the course of psychiatric illness. *Brit J Psychiatry* 1976; 129: 125–37.
7. Butzlaff RL, Hooley JM. Expressed emotion and psychiatric relapse: a meta-analysis. *Arch Gen Psychiatry* 1998; 55: 547–52.
8. Barrowclough C, Tarrier N. Psychosocial interventions with families and their effects on the course of schizophrenia: a review. *Psychol Med* 1984; 14: 629–42.
9. Lam DH. Psychosocial family intervention in schizophrenia: a review of empirical studies. *Psychol Med* 1991; 21: 423–41.
10. Kavaenagh D. Family interventions for schizophrenia. In: Kavenagh DJ, ed. *Schizophrenia: An Overview and Practical Handbook*. London: Chapman & Hall, 1992: 407–23.
11. Dixon L, Adamas C, Luckstead A. Update on family psychoeducation for schizophrenia. *Schizophrenia Bulletin* 2000; 26: 5–20.
12. Penn DL, Mueser KT. Research update on the psychosocial treatment of schizophrenia. *Am J Psychiatry* 1996; 153: 607–17.
13. Falloon IRH, Boyd JL, McGill CW et al. Family management in the prevention of exacerbations of schizophrenia. *N Engl J Med* 1982; 306: 1437–40.
14. Barrowclough C, Tarrier N. *Families of schizophrenic patients: cognitive behavioral intervention*. London: Chapman & Hall, 1992.
15. Mari JJ, Streiner DL. An overview of family interventions and relapse in schizophrenia: meta-analysis of research findings. *Psychol Med* 1994; 24: 565–78.
16. Martens L, Addington J. The psychological well-being of family members of individuals with schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* 2001; 36: 128–33.
17. Addington J, Addington D, Jones B. Family intervention in an early psychosis program. *Psychiatr Rehabil Skills* 2001; 5: 272–86.
18. Addington J, Collins A, McCleery A et al. The role of family work in early psychosis. *Schizophr Res* 2005; 79: 77–83.
19. Mueser KT, Gingerich S. *Alcohol and drug abuse, in coping with schizophrenia: a guide for families*. Oaklow: New Harbinger Publications, 1994.
20. Barrowclough C. Family intervention for substance use in psychosis. In: Graham HL, Copello A, Birchwood M, Mueser KT, eds. *Substance Misuse in psychosis: approaches to treatment and service delivery*. Chichester: John Wiley and Sons, 2003.
21. Barrowclough C, Haddock G, Tarrier N et al. Randomised controlled trial of cognitive behavioral therapy plus motivational intervention for schizophrenia and substance use. *Am J Psychiatry* 2001; 158: 1706–13.
22. McFarlane WR, Lukens E, Link B et al. Multiple family groups and psychoeducation in the treatment of schizophrenia. *Arch Gen Psychiatry* 1995; 52(8): 679–87.

23. Pilling S, Bebbington P, Kuipers E et al. Psychological treatments in schizophrenia: I. Meta-analysis of family intervention and cognitive behaviour therapy. *Psychol Med* 2002; 32: 763–82.
24. Mari JJ, Streiner DL. Family intervention for people with schizophrenia (Cochrane Review) In: The Cochrane Library. Oxford, UK: Update Software 1996; Issue 1.
25. Pharoah FM, Mari JJ, Streiner DL. Family intervention for people with schizophrenia (Cochrane Review) In: The Cochrane Library. Oxford UK: Update Software 1999; Issue.4.
26. Pitschel-Waltz G, Leucht S, Bauml J et al. The effect of family interventions on relapse and rehospitalisation in schizophrenia – a meta-analysis. *Schizophrenia Bulletin* 2001; 27: 73–92.
27. Leff JP, Kuipers L, Berkowitz R et al. A controlled trial of intervention with families of schizophrenic patients. *British Journal of Psychiatry* 1982; 141: 121–34.
28. Tarrier N, Barrowclough C, Vaughn C et al. The community management of schizophrenia: A controlled trial of a behavioural intervention with families: Two year follow up. *British Journal of Psychiatry* 1988; 154: 386–9.
29. Kottgen C, Soinnichen I, Mollenhauer K. Results of the Hamburg Camberwell Family Interview study, I-III. *Int J Family Psychiatry* 1984; 5: 61–94.
30. Falloon IRH, Boyd JL, McGill CW et al. Family management in the prevention of morbidity in schizophrenia: Clinical outcome of a 2 year longitudinal study. *Arch Gen Psychiatry*, 1985; 42: 887–96.
31. Leff JP, Kuipers L, Sturgeon D. A controlled trial of social intervention in the families of schizophrenic patients. *Br J Psychiatry* 1985; 146: 594–600.
32. Hogarty GE, Anderson CM, Reiss DJ et al. Family psychoeducation, social skills training and maintenance chemotherapy in the after care treatment of schizophrenia. One year effects of a controlled study on relapse and expresses emotion. *Arch Gen Psychiatry* 1986; 43: 633–42.
33. Hogarty GE, Kornblith SJ, Greenwald P et al. Three years trials of personal therapy with schizophrenics living with or independent of family 1: description of study and effects of relapse rates. *Am J Psychiatry* 1997; 154: 1514–24.
34. Tarrier N, Barrowclough C, Porceddu K et al. The Salford Family Intervention Project for Schizophrenic relapse prevention: five and eight year accumulating relapses. *Brit J Psychiatry* 1994; 165: 829–32.
35. Leff JP, Berkowitz R, Shavit A et al. A trial of family therapy versus relatives' groups for schizophrenia. *Brit J Psychiatry* 1990; 157: 571–7.
36. Mingyuan Z, Heqin Y, Chengde Y et al. Effectiveness of psychoeducation of relatives of schizophrenic patients: a prospective cohort study in five cities of China *Int J Men Health* 1993; 22: 47–59.
37. Randolph ET, Eth S, Glynn SM et al. Behavioral family management in schizophrenia: outcome of a clinic based intervention. *Brit J Psychiatry* 1994; 164: 501–6.
38. Xiong W, Phillips MR, Hu X et al. Family based intervention for schizophrenic patients in China: A randomised controlled trial. *Brit J Psychiatry* 1994; 165: 239–47.
39. Zhang M, Wang M, Li J et al. Randomised control trial family intervention for 78 first episode male schizophrenic patients: an 18 month study in Suzhou, Japan. *Brit J Psychiatry* 1994; 65 (Suppl 24): 96–102.
40. Zastowny RR, Lehman AF, Cole RE et al. Family management of schizophrenia: a comparison of behavioral and supportive family treatment. *Psychiatry Q* 1992; 63: 159–86.
41. Linszen D, Dingemans P, Vander Does JW et al. Treatment, expressed emotion and relapse in recent onset schizophrenia disorders. *Psychological Medicine* 1996; 26: 333–42.

42. Schooler NR, Keith SJ, Severe JB et al. Relapse and rehospitalisation during maintenance treatment of schizophrenia. The effects of dose reduction and family treatment. *Arch Gen Psychiatry* 1997; 54: 453–63.
43. Sellwood W, Barrowclough C, Tarrier N et al. Needs based cognitive behavioral family intervention for carers of patients suffering from schizophrenia: 12 month follow up. *Acta Scand Psychiatr* 2001; 104: 346–55.
44. Falloon I, Boyd J, McGill C. *The Family of Care of Schizophrenia*. London: Guilford, 1984.
45. Tarrier N, Lowson K, Barrowclough C. Cost-benefit analysis of a behavioural intervention with families of schizophrenic patients. *Br J Psychiatry* 1991; 159: 481–4.
46. Szmukler G, Kuipers E, Joyce J et al. An exploratory randomised controlled trial of a support program for carers of patients with a psychosis. *Soc Psychiatry Psychiatr Epidemiol* 2003; 38: 411–18.
47. Tarrier N, Barrowclough C, Haddock G et al. The dissemination of innovative cognitive-behavioral psychosocial treatments for schizophrenia. *J Men Health* 1999; 8: 569–82.
48. Hughes I, Hailwood R, Abbati-Yeoman J et al. Developing a family intervention service for serious mental illness: clinical observations and experiences. *J Men Health* 1996; 5: 145–59.
49. Fadden G. Implementation of family interventions in routine clinical practice following staff training programmes: a major cause for concern. *J Ment Health* 1997; 6: 599–612.
50. McFarlane WR, Dixon L, Lukens E et al. Family psychoeducation and schizophrenia: a review of the literature. *J Marital Fam Ther* 2003; 29: 223–45.
51. Corrigan VA, McCracken SG. Psychiatric rehabilitation and staff development: educational and organisational models. *Clin Psychol Rev* 1995; 15: 699–719.
52. Corrigan VA, McCracken SG. Refocussing the training of psychiatric rehabilitation staff. *Psychiatr Serv* 1995; 46: 1172–7.
53. Corrigan VA, McCracken SG, Edwards M et al. Collegial support and barriers to behavioural programs for severely mentally ill. *J Behav Ther Exp Psychiatry* 1997; 28: 193–202.
54. McCreddie RG, Phillips K, Harvey JA et al. The Nithscale schizophrenia surveys. VIII Do relatives want family intervention – and does it help? *Brit J Psychiatry* 1991; 158: 110–13.
55. Barrowclough C, Tarrier N, Lewis S et al. Randomised controlled effectiveness trial of a needs based psychosocial intervention service for carers of people with schizophrenia. *Brit J Psychiatry* 1999; 174: 505–11.
56. Mairs H, Bradshaw T. Implementing family intervention following training: what can the matter be? *J Psychiatr Mental Health Nurs* 2005; 12: 488–94.
57. Dixon L, Luckstead A, Stewart B, et al. Outcomes of the peer taught 12 week family to family education program for severe mental illness. *Acta Psychiatrica Scandinavica* 2004; 109: 207–15.
58. Kuipers E, Raune D. The early development of expressed emotion and burden in the families of first-onset psychosis. In Birchwood M, Fowler D, Jackson C, eds. *Early Intervention in Psychosis: A Guide to Concepts, Evidence & Interventions*. Chichester: John Wiley & Sons, UK, 2000.

A treatment approach to the patient with first-episode schizophrenia

Richard Drake and Shôn Lewis

There has been considerable recent research and clinical interest in early intervention in schizophrenia, underpinned by the idea that the earlier the intervention, the better the potential outcome. This begs the question as to how early is early, as it is clear that many people with schizophrenia have longstanding (probably largely inherited) brain vulnerabilities which manifest in non-specific ways until the evolution of frank psychotic symptoms. This vulnerability may undergo transition through a phase of nonspecific symptoms and behaviors, including social withdrawal, and anxiety and depression. The non-specific nature and poor positive predictive value of these types of symptom mitigate against pharmacological intervention until frank psychosis intervenes, although some researchers have used antipsychotics, antidepressants, and cognitive-behavioral therapy in those at particularly 'high risk' (see Box 15.1) to try to 'prevent' the evolution to frank psychosis.

The 'high risk' strategy remains controversial, and requires a careful balancing of risk and potential benefit after discussion with each individual patient. What is better established is the early treatment of frank psychotic symptoms once they evolve, and there have been attempts through health promotion and early recognition strategies to reduce the duration of untreated psychosis (DUP). Determining the DUP is necessary at presentation to confirm the presence of the temporal diagnostic criteria: 1 month for ICD-10 schizophrenia or DSM-IV schizophreniform disorder; or for DSM-IV schizophrenia, 1 month's psychosis (possibly less if treated), and 6 months of social dysfunction with prodromal or residual symptoms. Most patients present with

Box 15.1 Characteristics of people at 'high risk' for psychosis.

Yung et al ¹ Ultra high risk mental state

Attenuated (sub-threshold) psychotic symptom(s) over 1 week to 5 years
Trait schizotypal disorder or first-degree relative with schizophrenia plus
decrement of at least 30 points in global assessment of functioning (GAF)
over 1 month to 5 years
Brief Limited Intermittent Psychotic Symptoms (BLIPS): at least one psychotic
symptom for under 1 week in the past year
Any one of the following moderately predicts psychosis within 12 months:
trait + attenuated
trait or attenuated < 5 years
trait or attenuated or BLIPS and GAF <40
trait or attenuated or BLIPS and poor attention

Klosterkötter et al, ² Highest risk basic symptom criteria

Any one of the following weakly to moderately predicts psychosis within 9.6 years:
thought interference, perseveration, pressure or block
receptive dysphasia
difficulty distinguishing ideas & perception; or fantasy & memory
vague ideas of reference
derealization
subtle visual and auditory abnormalities

a DUP of a few weeks; but for some it will be months, and for a few, years. Median DUPs in Europe, Canada, and Australia are usually 2–6 months; but mean and median values from the US are often longer. Not only does a longer DUP predict worse symptomatic outcome but also recent studies have found this after adjustment for insidious onset or premorbid disability. The period of untreated psychosis is believed to be associated with accumulating symptomatic as well as social and interpersonal harm. It has been suggested that neurotoxic processes during this time can lead to cumulative long-term damage. Thus, shortening DUP may be of long-term benefit, apart from reducing distress.

Clinical assessment

A number of potential differential diagnoses need to be considered in the assessment of a patient with the first manifestation of psychotic symptoms: these are shown in Table 15.1. A thorough history must be obtained from the

Table 15.1 Differential diagnoses of ICD-10 schizophrenia ICD-10 diagnosis

Non-affective psychoses	Acute and transient psychotic disorders Schizoaffective disorder Persistent delusional disorder Induced or other persistent delusional disorder Manic, mixed or depressive episodes with psychotic symptoms Acute intoxication withdrawal with delirium drug induced psychotic disorder flashbacks e.g. due to: alcohol, illicit drugs, medications, lead, mercury Organic delusional disorder (schizophrenia-like) or delirium e.g.: epilepsy: partial seizures, partial complex status, peri- or inter-ictal psychoses; intracranial lesions: tumours, cysts, abscesses, malformations, haemorrhages (rarely stroke); connective tissue disorders, especially systemic lupus erythematosus; infections: syphilis, HIV, herpes simplex, other encephalitides; tuberculous meningitis, new variant CHD; metabolic causes: calcium, Wilson's disease; deficient B12, folate, niacin; metachromatic leukodystrophy, Nieman-Pick's etc.;
Affective psychoses	endocrine disorders: thyroid, glucocorticoid, etc.;
Drug induced psychoses	genetic causes: Huntingdon's chorea, velocardiofacial syndrome, etc.
Organic secondary psychoses	

Continued

Table 15.1 Differential diagnoses of ICD-10 schizophrenia ICD-10 diagnosis—cont'd

Dementias	Alzheimer's Vascular other; e.g. due to Pick's disease, Lewy-body disease, CJD
Personality disorder	Paranoid Schizoid Emotionally unstable, borderline-type Schizotypal disorder Autism
Schizotypy	Asperger's syndrome
Developmental disorders	other pervasive developmental disorders e.g. due to sub-acute sclerosing panencephalitis, metabolic causes
Neuroses	Dissociative disorder PTSD obsessive-compulsive disorder hypochondriacal disorder adjustment disorder
Feigning	Malingering (for identifiable advantage) Factitious Disorder (for no clear advantage in the presence of interpersonal abnormalities)

Table 15.2 Screening investigations in first-episode schizophrenia

<i>First line</i>	<i>Second line</i>
Neurological examination	CT/MRI scan
Complete blood cell count, ESR	Autoantibodies
Routine blood biochemistry, calcium	Syphilis serology
Thyroid function	HIV serology
Liver function	Chromosome studies
Electroencephalogram	Serum copper
Drug screen: urine or hair	Arylsulfatase-A
	CSF examination

ESR, erythrocyte sedimentation rate; CT, computed tomography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.

patient and corroborating information sought from any other sources available. These may include primary care staff, carers, and family, and perhaps police or social services. In some countries or communities community authority figures or traditional healers may have been consulted. A family history of psychotic disorder, history of substance use, and life events should be sought. Information from schools (or school leavers' reports in some countries) may be relevant.

A physical, including neurological, examination is essential. Investigations are listed in Table 15.2. Appropriate blood tests include full blood count, erythrocyte sedimentation rate (ESR), electrolytes, urea and calcium, liver function tests, thyroid function tests, and others as indicated, e.g. for syphilis. Since illicit substance use is widespread a urine drug screen is mandatory in most countries. Patients need an electrocardiogram (ECG) and computed tomography (CT) or magnetic resonance imaging (MRI) scan if there is any indication from the other information, e.g. if any neurological abnormality is suspected or the history is atypical. Some argue that these investigations are appropriate in all cases. In some areas lumbar puncture for cerebrospinal fluid is routine, depending on endemic infectious disease.

Careful symptom rating allows the tracking of clinical change over time. It is an increasingly important function in service and treatment evaluation. Outcome of first-episode schizophrenia can be measured in terms of severity of symptoms, social outcome, or by related constructs such as quality of life

or patient satisfaction. A variety of validated rating scales are available to the clinician, as outlined in Chapter 17. Attention should also be given to tracking of psychological health parameters, as discussed in Chapter 6.

Initial management: antipsychotic drugs

As discussed in Chapter 1, antipsychotics are the mainstay of management in first episodes as much as later ones, and since the evidence base is larger in established disease this may offer a guide to treatment where the evidence in first episodes is lacking or unclear. Moreover, to an extent this research sets the agenda for first-episode psychopharmacology.

Individuals in their first episode of schizophrenia are more susceptible to the motor side-effects of antipsychotics, which makes atypical antipsychotics an attractive option. However, in first episodes the evidence for superior efficacy of these agents is as yet mixed. Schooler et al³ found risperidone delayed relapse better in 555 participants randomized to risperidone or haloperidol; but at outcome both groups had the same level of symptoms. Lieberman et al⁴ reported that olanzapine reduced symptoms slightly better than haloperidol by most measures in a double-blind trial with 263 participants. A separate study in a Chinese population found that clozapine produced only slightly greater symptom reduction than chlorpromazine and no significant difference in the proportion 'recovering' after a year⁵. Preliminary data from a medium-sized trial suggest that quetiapine and risperidone do not differ in efficacy for positive symptoms in first-episode patients⁶.

Trials in established illness have recently found first and second generation antipsychotics equally effective^{7,8} and a smaller randomized trial in first-episode patients (about 60 patients per arm) suggests that second generation drugs are no more effective in clinical practice⁹. Thus, it is the lower burden of extrapyramidal effects that leads to many clinicians advocating the use of atypical antipsychotics in first-episode patients. There are also suggestions that these agents have benefits over the typical antipsychotics in the amelioration of negative and cognitive symptoms (see Chapters 3 and 4): they have been linked to better cognition in trials in first episode sufferers¹⁰, although this did not translate into better social function.

People in their first-episode of schizophrenia are likely to respond to lower doses of antipsychotics than those in later episodes, just as they are more sensitive to motor side-effects. Mean modal doses in trials have been about 3 mg of risperidone, 9–12 mg of olanzapine, 375 mg of quetiapine, and

2–5 mg haloperidol or 150–400 mg chlorpromazine. Notably, even some ‘prodromal’ patients have sometimes needed up to 15 mg olanzapine.

There are emerging concerns about metabolic side-effects of some second generation antipsychotics (perhaps clozapine and olanzapine most saliently) in first-episode patients (see Chapter 6). Many antipsychotics that are potent D2 blockers, including the atypicals risperidone and amisulpride, cause hyperprolactinemia and sexual side-effects. Again these need to be assessed and appropriate interventions taken should they intervene.

Antipsychotics in practice

From all these confusing findings one may draw several conclusions. There is some evidence that second generation drugs are superior and their use for first line treatment is preferred for reasons of tolerability. A scheme of typical initial doses of 0.5–1.0 mg risperidone or 2.5–5 mg olanzapine, increasing to initial treatment doses of 2 mg risperidone or 7.5–10 mg olanzapine, is relatively well evidenced. Recent evidence¹¹ implies that if absolutely no clinical response is seen to the treatment dose by a further 2 weeks or so, response is unlikely. This may prompt incremental increases towards the higher end of the treatment range, provided medication is well tolerated (e.g. about 4 mg risperidone or 15 mg olanzapine). If the drug is not well tolerated a switch may be made to a second line drug. It is clear that about 70% saturation of limbic D2 receptors is sufficient for treatment and motor side-effects can often be avoided by appropriate dosing. In that case anticholinergic drugs can be avoided, though in certain situations in the early stages it may well be prudent to prescribe them ‘as required’ to avoid motor side-effects, including dystonias and oculogyric crises, which can affect attitudes to medication and later adherence. Clearly there is a balance to be struck between safe treatment and minimizing risk of side-effects.

Other side-effects should be closely monitored, including blood lipids and considering the possibility of developing diabetic ketoacidosis. In part on the basis of concerns about motor, sexual, and metabolic side-effects, some clinicians use alternatives such as quetiapine (increasing to an initial treatment dose of about 400 mg, although somnolence may be a problem at first) or aripiprazole (initial treatment dose of 5 mg, going up to 10 mg) first line.

The use of mixtures of antipsychotics or adjunctive agents has been subjected to very little rigorous scientific scrutiny in first-episode patients. There is some evidence from patients with established illness that regular, adjunctive sodium valproate is beneficial when patients are violent.

Acute agitation

The management of acute agitation in schizophrenia is discussed in detail in Chapter 8. In first-episode patients particular care needs to be taken, given the potential for the distressing nature of any events to make later engagement with service providers difficult.

In terms of medication, benzodiazepines are often used as relatively safe short-term or ‘as required’ adjuncts for agitation or catatonic symptoms. An approach favored in the past was to use higher doses of oral typical antipsychotics, particularly those with antihistaminic properties. This is less safe and should be avoided as far as possible; as discussed in Chapter 8, atypical agents are being used more and more in these situations, with good effect.

For disturbance acute enough to require rapid tranquilisation, intramuscular (i.m.) antipsychotics and benzodiazepines are available. Consideration must be given to the risks of respiratory suppression when combining i.m. olanzapine and lorazepam; arrhythmias with i.m. haloperidol; or disinhibition by benzodiazepines without an antipsychotic. Zuclopenthixol acetate should generally not be used in first-episode patients, because of delayed onset, extended duration of action, and propensity to extrapyramidal side-effects.

Psychosocial and family intervention

Patients will need appropriate monitoring and support either in the community or hospital, depending on their symptoms, environment, ability to cooperate, and other risk-related behavior. Their carers need appropriate support too, especially if the patient stays in the community. Assessment of the resources available from their support network, its reliability and members’ needs is a key part of initial assessment and must continue throughout. Finding the appropriate support and setting may obviate the need for higher doses of antipsychotics.

The usual form of structured support for the family is by psychoeducation and behavioral problem solving¹², where possible with the involvement of a family support worker. It is particularly indicated in those with over 35 hours per week exposure to their carers. Key features include involvement of carers and patients, and sufficient duration of therapy.

As symptoms remit, evidence suggests that vocational and wider social functioning should be assessed. As outlined elsewhere in this book, interventions including occupational therapy, social skills training, cognitive remediation, and vocational intervention have been advocated, with varying degrees of success, in established schizophrenia. Packages including elements of these interventions form key parts of some of the complex interventions and services discussed below.

A large proportion of first-episode psychosis sufferers abuse alcohol and illicit drugs, which worsens every type of outcome. The sequence of engagement in services, persuasion and support to give up, and then maintain abstinence is critical. Specific interventions by specialist services may be needed, including motivational interviewing and pharmacotherapy (see Chapter 7). There is early evidence that cognitive-behavioral interventions can be beneficial for dealing with substance abuse in established schizophrenia¹³. Some have advocated fully integrated services for both psychosis and substance misuse but in practice sharing care between services is a common option.

Cognitive behavioral therapy (CBT) for those without substance dependence but with established schizophrenia can reduce residual psychopathology and there is some evidence of reduction in symptoms after first episodes, though the timing of the intervention needs to be individually tailored¹⁴. Psychodynamic psychotherapy at the acute stage probably worsens symptoms. Long-term supportive dynamic therapy may be beneficial but less so than assertive psychoeducational approaches¹⁵.

Management of initial uncertainty

Clinical uncertainty is not uncommon in the first-episode. In some cases it is unclear whether the patient is fully psychotic or merely has a mental state putting them at risk of frank psychosis. In other cases it is unclear whether they have an acute self-limiting, or drug-induced psychosis. In prodromal patients the long-term benefits of antipsychotics, especially compared with CBT or selective serotonin reuptake inhibitors (SSRIs), are uncertain. Acute psychotic disorders and drug-induced psychoses subside rapidly in most cases. On the other hand, delaying definitive treatment for schizophrenia seems to be harmful. How can this dilemma be resolved?

One approach is to discriminate on the basis of consequences and likelihood. The milder the symptoms, the more typical the picture of an 'at-risk' or drug-induced state or acute psychosis (often with a very short DUP and clear precipitant), the more likely one would wait-and-see. The more severe the symptoms, the less acute and the less typical of the above, the more likely one would treat-and-see. In the latter case, very rapid recovery would argue against schizophrenia but one might remain uncertain. Those who appear to have drug-induced psychosis but later achieve diagnoses of primary psychosis are more likely to have poor insight at presentation or carry a family loading for schizophrenia¹⁶. This is probably indicative of an underlying

‘psychosis proneness’ and the terms ‘drug precipitated’ psychosis might be apposite in such individuals.

Course and further treatment

Recovery from the first episode of positive symptoms is usual and 15–20% will not have another episode. Relapse, often with increasing disability and negative symptoms is, however, the most common pattern. At presentation certain factors can be identified that predict outcome, as shown in Box 15.2.

Recovery in the full sense of vocational and social rehabilitation, as well as symptom remission, should be the goal of treatment. However, evidence about how to achieve this in first-episode sufferers is only just emerging. Following remission, because of the high chance of relapse, long-term treatment and monitoring is indicated. Robinson et al¹⁷ found relapse occurring up to 5 years after presentation and so antipsychotic prophylaxis may be considered as long as this, although most clinical guidelines suggest a period of at least 1–2 years.

One-third to one-half of first-episode patients are non-adherent to prescribed medication during follow-up¹⁸. Poor adherence with treatment is if anything more problematic than at later stages of illness because placebo controlled trials show greater benefits of antipsychotics in first-episode treatment and first-relapse prevention. Robinson et al¹⁷ found that non-adherence increased the odds of relapse five-fold. Attention and time paid to therapeutic alliance at this stage may be repaid later on. A particular feature of insight – the recognition

Box 15.2 Predictors of poor outcome following first-episode psychosis.

- Being young at first onset
- Being male
- Having a low intelligence quotient (IQ)
- Manifesting severe negative symptoms at onset
- Exhibiting poor premorbid social adjustment
- Having a long duration of untreated psychosis (DUP)
- Experiencing insidious onset of symptoms
- Having a family history of schizophrenia
- Living in a high expressed emotion environment

that treatment has produced benefit – may have a particular importance for longer-term outcome¹⁹. As discussed in Chapter 10, compliance therapy, an intervention aimed at improving medication adherence based on motivational interviewing, showed early promise but replication has proved problematic²⁰.

There have therefore been efforts to find effective alternatives to long-term, full dose antipsychotics that patients might find more acceptable. Studies show low dose antipsychotics consistently lead to much more frequent relapse. One study attempted discontinuation after recovery and only in those who appear to stabilize: it found about half could not do so²¹. However, 20% of patients succeeded without relapse over 18 months. Comparing those trying to discontinue with those on continuous treatment, symptoms at follow-up are no worse and social function better if anything, though relapse rates were twice as high (20% compared with 40%). Relapses are associated with continuous illness and increased risk of suicide, as well as being disruptive, so this is not a trivial cost. Other studies demonstrate that intermittent treatment works better after first episodes than later ones; but only if patients are ready to restart medication at the first sign of symptoms, even if they are non-specific ones preceding psychosis. Therefore, this may indicate a suitable approach for some of those not agreeing to the safer option of full prophylaxis.

If patients fail to respond to a full dose of the initial antipsychotic for at least 6 weeks or cannot tolerate it then an alternative, preferably from a different class, should be substituted. The diagnosis should be reviewed, as should overall management, including psychosocial interventions. Factors like illicit drug use and adherence should be reconsidered. A depot antipsychotic formulation might be appropriate or supervision and rapidly dissolving formulations. Adjuvants like lithium (particularly for excitement or affective symptoms) should be considered. About 85% of patients respond in some way by this stage. If there is no response, despite the lack of evidence of superior efficacy of clozapine as first-line therapy, the evidence is most consistent with prescription of this antipsychotic drug in those likely to agree and comply (see Chapter 1).

Treating depression and anxiety

Though around a quarter of first-episode sufferers meet criteria for depression, many will recover and there is no evidence that antidepressants will help during active psychosis. Atypical antipsychotics may have some efficacy against mood

symptoms. However, for those who develop depression after their first episode or remain depressed after other symptoms have remitted, antidepressants may be indicated (e.g. SSRIs). Some may affect serum antipsychotic levels. CBT may be appropriate but there is no specific evidence for efficacy in this population (see also Chapter 5).

As discussed in Chapter 5, anxiety symptoms are common in schizophrenia, and can be disabling. In first-episode patients, particular attention should be paid to social anxiety symptoms, as this is a time of life when young people learn to socialize, and to establish their social networks.

Settings and services

Phase-specific first-episode or early intervention services allow staff to accumulate specialist experience and the service can be tailored to respond rapidly, diagnose appropriately and meet the needs of a group that includes a high proportion of young adults in the process of individuation and sensitive to stigma. Some first-episode services have been sited in shopping centers or have close ties to youth organizations and social services, in order to improve accessibility and reduce stigma.

First-episode services need to pay particular attention to engagement. This may mean making the services discrete from generic mental health services, and this has been adopted in some settings, although there is no evidence that such separation is crucial to efficacy. What appears to be most important is the offering of a series of high fidelity interventions targeting the needs of the individual, and respectful of their particular developmental and social context (as outlined below). The needs of carers and relatives also need to be met, including provision of education and support.

First-episode service effectiveness

There is accumulating evidence of benefit from first-episode services. Uncontrolled studies from Melbourne found instituting such a service improved a range of outcomes, though most patients were still hospitalized²². The specific role of early detection has been evaluated in a controlled prospective study comparing different areas in Scandinavia, one of which instituted a public education campaign and adapted services to shorten DUP. Results showed that reduced DUP could be achieved, from a median of 12 weeks to 4 weeks, but evidence that this translated into improved quality of life²³ or

reduced symptoms was lacking or inconsistent at 1-year follow-up (results at 2 years and later appear more promising). However, interpretation of this design is difficult because there was no blind rating and allowing for differences between areas is difficult.

Two randomized trials of full early intervention services are noteworthy. A randomized, controlled trial in Copenhagen (OPUS)²⁴ found benefits in symptom reduction and other outcomes with an enhanced first-episode service. This offered a wider range of treatments than the usual service, actively delivered. The Lambeth Early Onset (LEO) randomized, controlled trial in 144 first and second episodes in London²⁵ found an early intervention service improved service and reduced readmission rates at 18 months. Odds of relapse were halved but this was not significant, perhaps due to the sample size. There is as yet no evidence that early intervention alters the long-term course of illness for most patients, and a substantial proportion continue to have a poor illness trajectory.

There are some arguments against discrete first-episode services, e.g. that they fragment care for what may be a lifelong illness requiring continuing care: indeed, the transition to 'adult' services can be very difficult for the young person. Also, such services can divert resources from other services, sometimes even ones that this patient group will use later on. Staff in generic services can become de-skilled in the area of early episode psychosis management, and arguably end up with the residue of patients who don't get better. Also, most first-episode services target the young, and do not usually cater for older sufferers, such as those presenting with late-onset schizophrenia and many first episodes of delusional disorder. These patients may have quite different psychosocial needs and, certainly in adults over 60, may need lower doses of medication. Whatever the form of service offering care for first episodes, the accumulating evidence from first-episode service research does offer some guidance to what are appropriate approaches to individual patients.

Conclusions

The first-episode movement has gained a major following amongst clinicians and researchers. Whilst no one could argue against attempts to provide optimal care to people in this phase of illness, the evidence base for long-term benefits is lacking and many patients continue to require concerted ongoing management.

References

1. Yung AR, Phillips LJ, Yuen HP et al. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophr Res* 2004; 67: 131–42.
2. Klosterkötter J, Hellmich M, Steinmeyer EM et al. Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry* 2001; 58: 158–64.
3. Schooler N, Robinowitz J, Davidson M et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am J Psychiatry* 2005; 162: 947–53.
4. Lieberman JA, Tollefson G, Tohen M et al. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: A randomized double-blind trial of olanzapine vs haloperidol. *Am J Psychiatry* 2003; 160: 1396–404.
5. Lieberman JA, Phillips M, Gu H et al. Atypical and conventional antipsychotic drugs in treatment-naïve first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology* 2003; 28: 995–1003.
6. Gafoor R, Craig T, Power P et al. 8 week randomised trial of quetiapine versus risperidone: relative antipsychotic efficacies and side-effects. *Schizophr Res* 2006; 81(Suppl): 236.
7. Lieberman JA, Stroup S, McEvoy J et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; 353: 120.
8. Jones PB, Barnes TR, Davies L et al. Randomized controlled trial of effect on quality of life of second generation versus first generation antipsychotic drugs in schizophrenia – CUTLASS 1. *Arch Gen Psychiatry* 2006; 63: 1079–87.
9. Crespo-Facorro B, Perez-Iglesias R, Ramirez-Bonilla M et al. A practical clinical trial comparing haloperidol, risperidone, and olanzapine for the acute treatment of first-episode nonaffective psychosis. *J Clin Psychiatry* 2006; 67: 1511–21.
10. Harvey PD, Rabinowitz J, Eerdeken M, Davidson M. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. *Am J Psychiatry* 2005; 162: 1888–95.
11. Leucht S, Busch R, Hamann J et al. Early-onset hypothesis of antipsychotic drug action: a hypothesis tested, confirmed and extended. *Bio Psychiatry* 2005; 57: 1543–9.
12. Lenior ME, Dingemans PM, Linszen DH et al. Social functioning and the course of early-onset schizophrenia: five-year follow-up of a psychosocial intervention. *Brit J Psychiatry* 2001; 179: 53–8.
13. Haddock G, Barrowclough C, Tarrier N et al. Cognitive-behavioral therapy and motivational intervention for schizophrenia and substance misuse. 18-month outcomes of a randomised controlled trial. *Brit J Psychiatry* 2003; 183: 418–26.
14. Tarrier N, Lewis S, Haddock G et al. Cognitive-behavioral therapy in first-episode and early schizophrenia. 18-month follow-up of a randomised controlled trial. *Brit J Psychiatry* 2004; 184: 231–9.
15. Rosenbaum B, Valbak K, Harder S et al. Treatment of patients with first-episode psychosis: two-year outcome data from the Danish National Schizophrenia Project. *World Psychiatry* 2005; 5: 100–3.
16. Caton CL, Hasin DS, Shrout PE et al. Stability of early-phase primary psychotic disorders with concurrent substance use and substance-induced psychosis. *Brit J Psychiatry* 2007; 190: 105–11.
17. Robinson D, Woerner MG, Alvir MJ et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry* 1999; 56: 241–7.

18. Verdoux H, Lengronne J, Liraud F et al. Medication adherence in psychosis: predictors and impact on outcome. A 2-year follow-up of first-admitted subjects. *Acta Psychiatrica Scandinavica* 2000; 102: 203–10.
19. Drake RJ, Dunn G, Tarrier N et al. Insight as a predictor of the outcome of first-episode nonaffective psychosis in a prospective cohort study in England. *J Clin Psychiatry* 2007; 68: 81–6.
20. McIntosh AM, Conlon L, Lawrie SM, Stanfield AC. Compliance therapy for schizophrenia. *Cochrane Database Syst Rev* 2006; 3: CD003442.
21. Wunderink A, Nienhuis FJ, Sytema S et al. Targeted treatment revisited: results of an RCT in first-episode psychosis. *Schizophr Res Suppl* 2006; 255.
22. Power P, Elkins K, Adlard S et al. Analysis of the initial treatment phase in first-episode psychosis. *Br J Psychiatry Suppl* 1998; 172: 71–6.
23. Melle I, Haahr U, Friis S et al. Reducing the duration of untreated first-episode psychosis – effects on baseline social functioning and quality of life. *Acta Psychiatr Scand* 2005; 112: 469–73.
24. Petersen L, Jeppesen P, Thorup A et al. A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ* 2005; 331: 602.
25. Craig TK, Garety P, Power P et al. The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. *B M J* 2004; 329: 1067.

Treatment-resistant schizophrenia

*William D Spaulding, Robert W Johnson, Jeffrey R Nolting,
and Amanda Collins*

In the clinical and scientific literature, ‘treatment-resistant schizophrenia’ almost universally means not responsive to typical antipsychotics*. However, the meaning of ‘not responsive’ varies widely, ranging from ‘having no measurable impact on the illness’ to ‘suboptimal medication response’. People are usually deemed to have treatment-resistant schizophrenia if they are unresponsive to non-clozapine antipsychotics, even if they are responsive to clozapine or drugs not usually used to treat schizophreniform psychosis (e.g. anticonvulsants/mood stabilizers). There is no widely accepted theoretical rationale for linking treatment resistance to one class of drugs. Current terminological conventions reflect historical precedent (had atypical antipsychotics been discovered first, they would not be termed atypical). The meaning of being ‘resistant’ to one particular class of drug is further obscured by the tendency of psychiatric drugs to produce benefits across diagnostic boundaries (e.g. the mood stabilizing effects of some antipsychotics, and the antipsychotic effects of some mood stabilizers), and by recent findings that suggest non-clozapine atypicals are not superior to typicals for the reduction of psychotic symptoms¹.

*The terms ‘treatment resistant’ and ‘refractory’ are used synonymously in the clinical and scientific literature on schizophrenia. In early 2007 a PubMed scan of the National Library of Medicine for titles containing ‘treatment resistant schizophrenia’ since 1960 yielded 161 citations. ‘Refractory schizophrenia’ yielded 132. ‘Treatment refractory’ is technically redundant, because ‘not responsive to treatment’ is one definition of ‘refractory’ (Morris, ‘The American heritage dictionary of the English language’). However, the redundancy is widely used and accepted (71 of the titles containing ‘refractory schizophrenia’ in the PubMed scan use ‘Treatment refractory’). Since ‘treatment resistant’ appears slightly more popular, it will be used in this chapter.

Response to pharmacotherapy in schizophrenia is multidimensional, involving individually unique combinations of negative symptoms, positive symptoms, affective dysregulation, cognitive impairment, and other aspects of sociobehavioral functioning². Nevertheless, especially in controlled studies³, individuals are generally identified as treatment resistant based on diagnosis plus the presence of specific positive or negative psychotic symptoms, as measured by standardized structured interviews, after one or more formal trials of a typical antipsychotic. Inevitably, arbitrary cut-off points must be used to determine the level of severity that serves as the criterion for inclusion in the resistant group. Also, individuals sometimes show large differences in their responses to different typical antipsychotics, for reasons not well understood. Failing only one or two drug trials is therefore not a perfectly reliable criterion. These are manageable methodological problems when the research question is narrowly about whether one drug produces a better outcome than another, but they are significant impediments to a more complete understanding of the nature of treatment resistance. Perhaps most importantly, the methodological conventions of comparative drug trials can promote an implicit presumption that drug response (and, inversely, non-response) is a unidimensional 'either/or' dichotomy, when in fact it is a multiplicity of continuous dimensions, for both typical and atypical antipsychotics.

Moreover, it is generally acknowledged that schizophrenia itself is a heterogeneous category, probably not unified by a single set of causes. There are numerous etiological processes that operate in variable combinations to produce the many presentations of illness within the schizophrenia spectrum. Research is just beginning to articulate relationships between these factors and drug response⁴. Our perception of 'treatment resistance' reflects in part our inability to treat all possible processes and combinations. In addition, there are probably other biological factors, remote from the etiology of the illness itself, e.g. alleles that affect pharmacokinetics⁵, that contribute to treatment resistance in some individuals.

Considering the conceptual and methodological problems, it should not be surprising that the actual incidence of treatment-resistant schizophrenia has been difficult to ascertain. Although estimates vary widely, the proportion of people with schizophrenia who do not respond to antipsychotic medication at all is at least 20%⁶. Estimates of the effectiveness of clozapine for people whose illness is resistant to typicals range from 30 to 60%. Atypicals other than clozapine do not appear to be more effective than typicals¹, although

they are still presumed to be safer. The evidence that valproic acid enhances the effectiveness of antipsychotic medication is sufficient that the Food and Drug Administration (FDA) has approved it for such use. Research on other mood stabilizers is promising, but so far none has been approved.

As treatment for schizophrenia expands beyond pharmacotherapy and other biological approaches, the implications of being refractory to biological treatment are changing. There is no longer any doubt that psychosocial treatment substantially improves outcome beyond that achieved with medication alone⁷ (see Chapters 2, 3, and 17). Among people whose illness is resistant to typical antipsychotics, clozapine enhances their chances of benefiting from psychosocial treatment⁸, but this does not mean that psychosocial treatment is always dependent on successful pharmacological treatment. Specialized types of cognitive behavioral therapy can help with medication-resistant hallucinations and delusions^{9,10} (see Chapter 2). The putative benefits of the atypical risperidone for cognitive functioning (relative to typicals) appear to be overwhelmed and obscured by the benefits of a comprehensive psychiatric rehabilitation program¹¹ (Chapter 4). Intensive psychiatric rehabilitation is effective for people for whom medication has been ineffective or insufficient^{12,13}. Silverstein et al¹³ propose that these findings indicate that the proportion of people diagnosed with schizophrenia who are treatment resistant is substantially smaller than generally believed, because 'resistant' has meant only resistant to pharmacotherapy.

For practical purposes, the concept of treatment resistance needs to incorporate more than just medication response, and it needs to include dimensions of personal and social functioning beyond those of interest in antipsychotic drug trials. Most importantly, it needs to give clinicians solutions that are more helpful than waiting for the research to generate better medications. A complete reformulation of the concept has not yet been accomplished, and would be well beyond the scope of this chapter, but hopefully the near future will see systematic work toward that end. Meanwhile, it is useful to identify specific clinical tools and the types of treatment resistance for which they may be helpful. That is the organizational scheme for the remainder of this chapter. Most of the tools discussed elsewhere in this book are potentially effective for drug treatment-resistant schizophrenia. The tools listed here (summarized in Box 16.1) are ones that are especially important for directly addressing treatment resistance, and for making other treatments accessible to patients whose illnesses are otherwise treatment resistant.

Box 16.1 Seven tools for use in treatment resistance.

Medication algorithms
 Neuropsychological therapy and environmental engineering
 Contingency management
 Cognitive behavioral therapy for treatment-resistant psychotic symptoms
 Systematic, expanded and individualized assessment of pharmacotherapy
 Therapeutic jurisprudence
 Risk assessment and risk management

Seven clinical tools for managing treatment resistant schizophrenia

Medication algorithms

Research criteria for identifying medication resistance are generally unhelpful in clinical practice³. Medication algorithms¹⁴ are proposed as alternative tools for determining optimal medication regimens for people whose illness does not respond well to initial treatment attempts (see Chapter 1). It is too early in the development of medication algorithms, and psychopharmacology is progressing too rapidly to be confident about exactly how such algorithms will work, even in the near future. However, considering existent algorithms in the context of current trends, it is likely that the steps toward identifying medication resistance will approximate this sequence ('trials' means trials of sufficient time, with titration to maximum dose, which are often difficult to accomplish in clinical practice; the reader is also referred to Figures 1.1 and 1.2 in Chapter 1 for treatment algorithms, and Tables 1.2 and 1.3 for details of different medications, including recommended doses):

- (1) Trials of first recourse agents, including one or more atypical D2 antagonists (risperidone, olanzapine, ziprasidone, quetiapine, etc.) and a D2 partial agonist (e.g. aripiprazole);
- (2) A trial of atypical antipsychotic augmented by a mood stabilizer;
- (3) A trial of an injectable depot preparation of an atypical (this step may come earlier when adherence is a suspected factor: see also Chapter 1 for details of available depots, and Chapter 10 for a broader discussion of adherence);
- (4) Trials of combinations of atypical antipsychotics;

- (5) A trial of typical antipsychotic (some practitioners would forego this step, as in Chapter 1);
- (6) A trial of clozapine (see Chapter 1 for details of clozapine);
- (7) Trials of typical/atypical combinations (refer to Chapter 1).

Steps 4 and 7 will probably generate the most controversy as algorithms evolve. Polypharmacy is a recognized problem⁶ and algorithms are designed to avoid it. There is no widely accepted theoretical model for selecting antipsychotic combinations, nor even agreement about whether a rational/theoretical approach would be better than a strictly empirical or even intuitive approach.

Neuropsychological therapy and environmental engineering

Even when pharmacotherapy is effective at reducing the cognitive disorganization of acute psychosis, stabilized and optimally medicated patients often have significant residual neurocognitive impairment. In this sense, all or most post-acute impairment is treatment resistant. Such impairment is a strong limiting factor in rehabilitation success. A number of neuropsychological approaches to directly treating the neurocognitive impairments of schizophrenia have been recently developed (see Chapter 4). They range from computer-based tasks that exercise basic attention and memory to group-format techniques that enhance social perception and problem solving. Outcome measures that have shown effects of neuropsychological therapy range from social competence through psychotic symptoms to work performance (see also Chapters 11 and 12). A meta-analysis of 17 controlled neuropsychological therapy trials¹⁵ supports the approach's effectiveness. This type of therapy appears to benefit patients across the spectrum of severity, treatment resistant or not, but for treatment-resistant patients it could be a crucial determinant of further recovery.

A similar approach, based on operant learning principles, has proven effective in helping people with severe neurocognitive impairment¹⁶. In this approach, individuals are systematically reinforced with tokens as they successively approximate motor behaviors prerequisite to group participation, such as appropriate motor orientation, eye contact, disregard of ambient distraction, and performance of elemental group-related tasks. This approach is thought to be especially important for people who have the most severe disabilities and functional limitations, who may not otherwise be able to participate in conventional skill training.

There is some overlap between techniques that address neuropsychological functioning and techniques used in cognitive behavioral therapy (CBT) and social skills training (discussed in Chapter 12). Integrated packages sometimes include evidence-based techniques from multiple domains. For example, since the 1980s social skills training materials have incorporated the CBT technique of structured problem solving, and have included strategies for doing social skills training with people who have neurocognitive impairments. Integrated psychological therapy (IPT)¹⁷ is an evidence-based exemplar that integrates all three techniques in a group skill training format. Meta-analysis¹⁸ suggests that IPT is more effective than standard treatment for symptom reduction, psychosocial functioning, and neurocognition in adults with schizophrenia. The benefits appear across multiple outcome measurement domains, including psychological testing, self-report, and clinician ratings, and are independent of treatment setting (inpatient versus outpatient, academic versus non-academic) and stage of illness (acute versus chronic). Moreover, the benefits appear to increase or accumulate over time. The neuropsychological components of IPT contribute uniquely to overall outcome¹⁹. Cognitive enhancement therapy (CET) is a package similar to IPT, with empirical evidence of effectiveness²⁰.

High-intensity psychiatric rehabilitation programs such as described by Spaulding et al¹⁹ and Silverstein et al¹³ have non-specific benefits for neuropsychological functioning, even without components that explicitly target cognitive impairment. People with treatment-resistant illnesses disproportionately find themselves in such programs, so non-specific treatment effects on neurocognitive impairment should be expected to be an important factor in such people's success in moving to less intensive and less restrictive settings.

Neurocognitive impairments that do not respond to treatment can nevertheless be managed through specialized environmental engineering that provides compensatory supports^{21–23} (see Chapter 4). This approach involves environmental modifications, ranging from sound proofing (to reduce auditory distraction) to packaging wardrobe elements for daily use (to compensate for disinhibition and deficits in executive cognition). Such interventions have been shown to enhance routine daily functioning and adherence to treatment, both of which provide a demonstrable contribution to rehabilitation progress and recovery. However, it is important to exercise caution when employing these solutions to ensure that they are not being used when a rehabilitative approach would re-establish more normal cognitive and behavioral functioning, and greater independence.

Related compensatory approaches aim to create environmental supports that reduce cognitive burdens, stress, and requirements for functioning while providing for the individual's needs and quality of life²⁴. In a sense, broader approaches such as assertive community treatment (ACT) and supported employment are examples of compensatory environmental engineering. Although they are not based on neuropsychological considerations, they do aim to compensate for deficits in behavioral functioning with extraordinary environmental features.

Contingency management

Contingency management is a genre of techniques that evolved from learning and social-learning theories in the 1960s. They are especially important in non-acute psychiatric inpatient and residential settings, where people with treatment-resistant conditions are disproportionately represented²⁵. In fact, in many modern mental health systems, such settings are populated solely by people with conditions that are resistant to pharmacotherapy. The consistent effectiveness of contingency management in these settings makes this approach especially important for treatment-resistant schizophrenia.

The earliest applications of contingency management for schizophrenia, in the form of token economies in psychiatric hospitals, provided strong empirical evidence of effectiveness in promoting adaptive behavior²⁶. In a 7-year controlled clinical outcome trial²⁷ described at the time as 'the largest outcome trial in the history of psychiatry', a social learning-based rehabilitation program that included contingency management was vastly superior to psychiatric treatment as usual. It was also superior to an enriched version of therapeutic community, a psychosocial approach that was popular in psychiatric and substance abuse settings in the 1960s and 1970s. Replication studies and an accumulation of case studies and institutional experience continues to support the effectiveness of contingency management in replacing inappropriate behavior (including psychotic symptoms), with adaptive behavior and increasing participation in treatment and rehabilitation^{12,13,28}. In its modern form, contingency management is a more highly individualized and targeted treatment than in the early token economies. In addition, it typically involves extensive interaction between the identified patient and therapist(s), with negotiations and contracts to link specific rewards and other consequences to specific desired behaviors²⁹. Highly individualized contingency management interventions are often termed behavior management programs (BMPs).

As psychiatric rehabilitation has evolved, the role of contingency management in enhancing engagement in therapeutic activities has become increasingly important³⁰. The original goal of promoting adaptive behavior can now be more extensively operationalized, in terms of engagement and participation in social skills training, occupational/vocational activities, and the various other psychosocial modalities discussed in this book. In this sense, contingency management addresses and compensates for what may be the most malignant and pervasive consequence of resistance to pharmacotherapy, failure to engage in psychosocial treatment and rehabilitation. When combined with other social-learning modalities, contingency management has been shown to be specifically effective with two of the most troublesome and drug-resistant problems encountered in mental health settings, namely aggression^{31,32} (see Chapter 8 for a discussion of treatment of aggression in schizophrenia) and polydipsia³³. Most recently, contingency management is being applied to co-occurring substance abuse, frequently a barrier to recovery from SMI^{34,35} (see Chapter 7).

Cognitive behavioral therapy for treatment-resistant psychotic symptoms

As outlined in Chapter 2, specialized forms of CBT show robust effects on drug treatment-resistant hallucinations^{9,10}. Delusions, which are generally more resistant to psychopharmacotherapy, can also be effectively resolved. In real world clinical settings the efficacy of these approaches may often be compromised by other common features of treatment-resistant psychosis, most notably inability or unwillingness to engage in therapeutic activities. Depending on the underlying causes, responsiveness to CBT may be dependent on other treatments, most notably neuropsychological therapy and contingency management.

The focus of CBT on the person's perceptions and beliefs is producing a convergence with two other important developments in services for people with treatment-resistant SMI. The first is motivational interviewing (MI)³⁶, a dyadic therapy technique designed to clarify the person's values and desires in a way that motivates the person toward positive change. MI is highly compatible with CBT and other psychiatric rehabilitation approaches, and has been demonstrated to be helpful for people with SMI by enhancing engagement in substance abuse treatment³⁷ and adherence to and maintenance of a rehabilitation regimen^{38,39}. Substance abuse and adherence are significant factors in treatment-resistant schizophrenia and are covered in more detail in Chapters 7 and 10, respectively.

The second converging factor is the recovery concept⁴⁰, promoted by a consumer-based movement that rejects many of the implications of a medical model view of mental illness. In the recovery perspective, the very notion of treatment resistance is an artifact of a flawed paradigm overly dependent on medical treatment. Convergence of CBT and MI techniques with recovery concepts could in the near future produce a new, holistic approach to treatment resistance in which the identified patient gains a greater degree of personal control over the illness and its disabilities, transcending limitations of pharmacology and other treatment technologies. This would transform the meaning, much less the treatment, of treatment-resistant schizophrenia, even beyond the transformation envisioned by Silverstein et al¹³.

Systematic, expanded, and individualized assessment of psychopharmacotherapy

Ordinarily, prescription of antipsychotic medication is based on a relatively brief clinical interview, sometimes with corroborating information from the patient's social environment. The data produced by this approach can be so unreliable that they prevent an accurate assessment of drug effects, or even of the target symptoms themselves. In the terminology of experimental design, this creates a low power test, vulnerable to type 2 error (failing to detect an effect when it is in fact present). A type 2 error creates in turn the appearance of treatment resistance. Once an illness is perceived to be drug resistant, prescribing practice becomes driven by the prescriber's liability management and related factors, if it is rational at all. This often leads to the pervasive problem of polypharmacy⁶ which further obscures drug effects. Increasing the measurement power of the drug trial prevents this cascade and helps discriminate between true treatment resistance and drug effects that are subtle, unusual, outside the usual domains of psychopharmacological assessment, or otherwise difficult to detect.

The power of psychopharmacological assessment should first be increased by expanding the database beyond subjective report and historical records. This requires resources not common in real world mental health settings, but people with drug-resistant psychosis often find themselves in environments where expanded, milieu-based assessment is more feasible, such as inpatient and residential settings. In such settings, where there are high proportions of people with drug-resistant psychosis, investment in expanded assessment capabilities is well justified. Expansion should include use of standardized measures that quantify the information a prescriber would normally collect

anecdotally, such as the Brief Psychiatric Rating Scale (BPRS)⁴¹. Outside the consulting room, standardized observational measures such as the Nurses Observational Scale for Inpatient Evaluation (NOSIE)⁴² provide quantitative data on the patient's behavior in the ambient environment, often quite different from behavior in a structured interview. The Time-Sample Behavioral Checklist (TSBC)⁴³ is a related observational measure that provides even more precise behavioral data relevant to evaluation of medication effects.

In treatment settings where staff are trained to implement contingency management, systematic quantitative observation of highly specific behaviors is routine, and is easily adapted to the purposes of a drug trial. Behavior management programs (BMPs) provide precise data on the frequency and quality of specific target behaviors, including medication-responsive behaviors.

Rehabilitation-oriented treatment settings also generate data in domains not conventionally associated with drug trials, as shown in Box 16.2, and which should be crucial targets for assessing functional responses to treatment. For example, the Independent Living Skills Inventory (ILSI)⁴⁴ provides information on a person's ability to perform domain specific skills required for successful community living, such as money management, cooking, occupational skills, etc. Using such data within the context of thoughtfully designed naturalistic drug trials affords more reliable assessment and measurement of the etiology of the resistance and increases the probability of detecting significant drug effects on an individual's functioning, whose illness might otherwise be deemed drug-treatment resistant.

Another way to increase the power of a drug trial is to amplify the longitudinal dimension of measurement. All of the clinical measures discussed above are well suited to repeated administration over time. The residential and inpatient settings in which people with treatment-resistant schizophrenia are often treated are usually well suited to frequent longitudinal data collection.

Box 16.2 Broader outcomes in rehabilitation settings.

- Following daily routines
- Participating in occupational activities
- Managing personal finances
- Engaging in social activities

Availability of longitudinal data enhances evaluation not only of medication effects but also overall progress in rehabilitation. This is crucial to optimizing an individual rehabilitation and recovery plan. An administrative commitment to systematic collection and analysis of longitudinal behavioral data may be one of the most important aspects of treating treatment-resistant schizophrenia. Chapter 17 provides further assessment tools that can be used in clinical practice.

Therapeutic jurisprudence

Therapeutic jurisprudence (TJ) is a set of principles and techniques intended to use the law to benefit and enhance mental health⁴⁵. TJ is especially relevant to treatment-resistant schizophrenia, because of the frequency with which the latter is accompanied by legal complications such as civil commitment, issues of competency (see Box 16.3), and court-ordered treatment^{47,48}. It is increasingly necessary for clinicians who treat people with treatment-resistant psychoses to be proficient in dealing with legal complications and making good therapeutic use of legal processes and mechanisms. This includes collaborating with:

- legal authorities and rehabilitation teams to make optimal clinical use of relevant legal processes and mechanisms;
- legal authorities, consumers, advocates, and policy makers to make mental health law and its implementation conducive to rehabilitation and recovery;
- legal authorities to educate consumers, advocates, legal professionals, and mental health professionals in therapeutic jurisprudence.

Box 16.3 Five steps for assessing competence.

Patient registers information provided

Patient absorbs, retains, and recalls this information

Patient understands the information is relevant to them in that they appreciate that decisions they make will have certain consequences for them (cognitive understanding)

Patient makes decisions about the consequences of decisions compatible with their own values and beliefs (evaluative understanding)

Patient communicates their understanding and the decisions based on that understanding

Based on reference 45.

Risk assessment and risk management

People with treatment-resistant schizophrenia are disproportionately found by a legal authority, at some point in time, to be dangerous to themselves and/or others. Safely serving these people in the least restrictive and most integrated settings possible, particularly community settings, requires highly reliable assessment and management of the consequent risks. Historically, mental health professionals' ability to predict dangerousness has been dubious, but the past decade has seen crucial advances in the relevant technology⁴⁹. Effective treatment and rehabilitation for treatment-resistant serious mental illness will require the best risk assessment and management that science and technology can provide. This means explicit evaluation of a person's potential for dangerousness, under existing circumstances and under circumstances anticipated in the foreseeable future (it is no longer acceptable to say simply that a person is not dangerous right here and right now). This includes review and interpretation of the person's social history, use of appropriate psychometric and actuarial instruments, and functional assessment of the person's psychiatric disorder.

Risk management requires a complete risk assessment plus a complete enumeration of the conditions, circumstances, and environments that could precipitate behavior wherein the patient is considered to be dangerous to himself or others in the future, and a plan for minimizing those risks. For a full discussion of these issues, see Chapter 9.

Conclusion

Although good drug response enhances success in psychosocial treatment, the latter is not necessarily dependent on the former for effectiveness. Some specific treatments succeed where pharmacotherapy fails, although this does not mean that the mechanisms of treatment response or the actual outcome is exactly the same. Management of these complications is not an easy task for the treatment team; the use of both medication algorithms and more general algorithms for treatment and rehabilitation of schizophrenia⁵⁰ is essential. Comprehensive multimodal psychiatric rehabilitation⁵¹ is the best available solution for people who have pervasive difficulty with following daily routines and performing the basic activities of daily living, whether or not those difficulties are associated with poor response to pharmacotherapy. Contingency management has been shown to be a highly effective component of rehabilitation, especially in settings where people with drug-resistant illnesses

are disproportionately represented. Moreover, those settings can produce enriched data on behaviors not typically associated with drug trials, but which might be crucial targets for assessing treatment response.

Research that focuses on patients' perceptions, beliefs, and decision-making processes is needed. Although these processes are not well studied, they may well be important components of the psychological factors that contribute to treatment resistance. They are influenced by both external factors (e.g. hospital staff perceptions) and internal factors (e.g. self-attributions). It is likely that the richest data informing interventions that address treatment resistance will be garnered from research in this domain, including research on beliefs about the illness and its consequent disabilities, and especially about the person's prospects for recovery.

References

1. Lieberman JA, Stroup TS, McEvoy JP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; 353: 1209–23.
2. Lindenmayer JP. Treatment refractory schizophrenia. *Psychiatr Q* 2000; 71(4): 373–84.
3. Brambilla P, Barale F, Caverzasi E et al. Clozapine-treated subjects with treatment-resistant schizophrenia: a systematic review of experimental and observational studies. *Int Clin Psychopharmacol* 2002; 17(4): 189–95.
4. Molina V, Reig S, Sarramea F et al. Anatomical and functional brain variables associated with clozapine response in treatment-resistant schizophrenia. *Psychiatry Res* 2003; 124(3): 153–61.
5. Kawanishi C, Furuno T, Kishida I et al. A patient with treatment-resistant schizophrenia and cytochrome P4502D6 gene duplication. *Clin Genet* 2002; 61(2): 152–4.
6. Stahl SM, Grady MM. A critical review of atypical antipsychotic utilization: comparing monotherapy with polypharmacy and augmentation. *Curr Med Chem* 2004; 11(3): 313–27.
7. Mojtabai R, Nicholson RA, Carpenter BN. Role of psychosocial treatments in management of schizophrenia: A meta-analytic review of controlled outcome studies. *Schizophr Bull* 1998; 24(4): 569–87.
8. Rosenheck R, Tekell J, Peters J et al. Does participation in psychosocial treatment augment the benefit of clozapine? Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. *Arch Gen Psychiatry* 1998; 55(7): 618–25.
9. Rector NA, Beck AT. Cognitive behavioral therapy for schizophrenia: An empirical review. *J Nerv Ment Dis* 2001; 189(5): 278–87.
10. Zimmermann G, Favrod J, Trieu V et al. The effect of cognitive behavioral treatment on the positive symptoms of schizophrenia spectrum disorders: A meta-analysis. *Schizophr Res* 2005; 77(1): 1–9.
11. Liberman R, Gutkind D, Mintz M et al. Impact of risperidone versus haloperidol on activities of daily living in the treatment of refractory schizophrenia. *Compr Psychiatry* 2002; 43(6): 469–73.
12. Paul G, Mendiola A. Effectiveness of inpatient treatment programs for mentally ill adults in public psychiatric facilities. *Appl Prev Psychol* 1992; 1(1): 41–63.

13. Silverstein S, Hatashita-Wong M, Wilkniss SM et al. Behavioral rehabilitation of the "treatment-refractory" schizophrenia patient: conceptual foundations, interventions and outcome data. *Psychol Serv* 2006; 3: 145–69.
14. Chiles JA, Miller AL, Crimson ML et al. The Texas medication algorithm project: Development and implementation of the schizophrenia algorithm. *Psychiatr Serv* 1999; 50(1): 69–74.
15. Twamley EW, Jeste DV, Bellack AS. A review of cognitive training in schizophrenia. *Schizophr Bull* 2003; 29(2): 359–82.
16. Silverstein SM, Menditto A, Stuve P. Shaping attention span: an operant condition procedure for improving neurocognitive functioning in schizophrenia. *Schizophr Bull* 2001; 27: 247–57.
17. Brenner H, Roder V, Hodel B et al. Integrated psychological therapy for schizophrenic patients. Toronto: Hogrefe & Huber, 1994.
18. Roder V, Mueller DR, Mueser KT et al. Integrated Psychological Therapy (IPT) for schizophrenia: Is it effective? *Schizophr Bull* 2006; 32(S1): S81–S93.
19. Spaulding WD, Reed D, Sullivan M et al. Effects of cognitive treatment in psychiatric rehabilitation. *Schizophr Bull* 1999; 25(4): 657–676.
20. Hogarty GE, Flesher S, Ulrich R et al. Cognitive enhancement therapy for schizophrenia: effects of a 2-year randomized trial on cognition and behavior. *Arch Gen Psychiatry* 2004; 61(9): 866–76.
21. Goldberg J. Cognitive retraining in a community psychiatric rehabilitation program. In Spaulding W, ed. *Cognitive technology in psychiatric rehabilitation*. Lincoln, NE: University of Nebraska Press, 1994: 67–86.
22. Heinssen R. The cognitive exoskeleton: environmental interventions in cognitive rehabilitation. In Corrigan P, Yudofsky S, eds. *Cognitive Rehabilitation of Neuropsychiatric Disorders*. Washington DC: American Psychiatric Press, 1996: 395–424.
23. Velligan D, Bow-Thomas L, Huntzinger C et al. Randomized controlled trial of the use of compensating strategies to enhance adaptive functioning in outpatients with schizophrenia. *Am J Psychiatry* 2000; 157: 1317–23.
24. Velligan DI, Bow-Thomas CC. Two case studies of cognitive adaptation training for outpatients with schizophrenia. *Psychiatr Serv* 2000; 51(1): 25–9.
25. Corrigan PW, Liberman RP, eds. *Behavior Therapy in Psychiatric Hospitals*. New York: Springer, 1994.
26. Ayllon T, Azrin NH. *The Token Economy*. New York: Appleton-Century-Crofts, 1968.
27. Paul GL, Lentz RJ. *Psychosocial treatment of chronic mental patients: Milieu vs. social learning programs*. Cambridge, MA: Harvard University Press, 1977.
28. Wong S, Massel H, Mosk M et al. Behavioral approaches to the treatment of schizophrenia. In Burroughs G, Norman T, Rubenstein G, eds. *Handbook of Studies on Schizophrenia*. Amsterdam: Elsevier Science Publishers, 1986: 79–100.
29. Heinssen R, Levendusky P, Hunter R. Client as colleague: therapeutic contracting with the seriously mentally ill. *Am Psychol* 1995; 50(7): 522–32.
30. Heinssen RK. Improving medication compliance of a patient with schizophrenia through collaborative behavioral therapy. *Psychiatr Serv* 2002; 53: 255–7.
31. Beck N, Greenfield S, Gotham H et al. Risperidone in the management of violent, treatment-resistant schizophrenics hospitalized in a maximum security forensic facility. *J Am Acad Psychiatry Law* 1997; 25: 461–8.
32. Beck NC, Menditto AA, Baldwin L et al. Reduced frequency of aggressive behavior in forensic patients in a social learning program. *Hosp Community Psychiatry* 1991; 42: 750–2.
33. Baldwin L, Beck N, Menditto A et al. Decreasing excessive water drinking by chronic mentally ill forensic patients. *Hosp Community Psychiatry* 1992; 43: 507–9.

34. Sigmon SC, Higgins ST Voucher-based contingent reinforcement of marijuana abstinence among individuals with serious mental illness. *J Subst Abuse Treat* 2006; 30(4): 291–5.
35. Strong Kinnaman JE, Slade E, Bennett ME et al. Examination of contingency payments to dually-diagnosed patients in a multi-faceted behavioral treatment. *Addict Behav* 2007; 32: 1480–5.
36. Miller WR, Rollnick S. *Motivational interviewing: Preparing people for change*, 2nd edn. New York: The Guilford Press, 2002.
37. Carey KB, Carey MP, Maisto SA et al. The feasibility of enhancing psychiatric out-patients' readiness to change their substance use. *Psychiatr Serv* 2002; 53(5): 603–8.
38. Kemp R, Hayward P, Applewaite G et al. Compliance therapy in psychotic patients: Randomised controlled trial. *BMJ* 1996; 312: 345–9.
39. Kemp R, Kirov G, Everitt B et al. Randomized controlled trial of compliance therapy: 18-month follow-up. *Br J Psychiatry* 1998; 173: 271–2.
40. President's New Freedom Commission on Mental Health. Report to the President (2004). [cited 2004 Oct 15] Available from: <http://www.mentalhealthcommission.gov/reports/reports.htm>.
41. Ventura J, Green M, Shaner A et al. Training and quality assurance with the BPRS. *Int J Meth Psychiatr Res* 1993; 3: 221–44.
42. Honigfeld G, Gillis RD, Klett CJ. Nurses' observation scale for inpatient evaluation: a new scale for measuring improvement in chronic schizophrenia. *J Clin Psychol* 1965; 21: 65–71.
43. Paul GL, ed. *Observational assessment instrumentation for service and research: The time-sample behavioral checklist for assessment in residential settings (part 2)*. Champaign, IL: Research Press, 1987.
44. Menditto AA, Wallace, CJ, Liberman RP et al. Functional assessment of independent living skills. *Psychiatri Rehabil Skills* 1999; 3: 200–19.
45. Daicoff S, Wexler B. Therapeutic jurisprudence. In: Goldstein A, ed. *Handbook of Psychology: Forensic Psychology*. New York: John Wiley & Sons, 2003: 561–80.
46. Pargiter and Cloverdale, 2001.
47. Spaulding W, Poland J, Elbogen E et al. Therapeutic jurisprudence in psychiatric rehabilitation. *Cooley Law Review* 2000; 17: 135–70.
48. Elbogen E, Tomkins A. The psychiatric hospital and therapeutic jurisprudence: applying the law to promote mental health. In Spaulding W, ed. *New Directions for Mental Health Services, The State Hospital in the 21st Century*. San Francisco, CA: Jossey Bass, 1999; 89: 71–84.
49. Bauer A, Rosca P, Khawalled R et al. Dangerousness and risk assessment: the state of the art. *Isr J Psychiatry Relat Sci* 2003; 40: 182–90.
50. Spaulding WD, Johnson DL, Coursey RD. Combined treatments and rehabilitation of schizophrenia. In: Sammons MT, Schmidt NB, eds. *Combined Treatments for Mental Disorders*. Washington DC: American Psychological Association, 2001: 161–90.
51. Spaulding WD, Sullivan ME, Poland JS. *Treatment and Rehabilitation of Severe Mental Illness*. New York: Guilford, 2003: 154–6.

Rating scales in schizophrenia: clinical applicability

Marc Corbière and Tania Lecomte

Clinicians are increasingly asked to offer evidence-based practices and to demonstrate the efficiency and efficacy of their chosen treatment regimens, necessitating the use of specific measures and rating scales. Rating scales are also useful for many clinical purposes, such as determining specific client profiles, deficits, symptoms, needs, and skills. Evaluations in the field of psychiatry are often complex because of the various aspects needing to be considered such as patients' characteristics, behaviors, cognitive deficits, motivations, symptoms, and physical issues. Furthermore, the individual's mental, physical, and emotional states need to be taken into consideration prior to conducting an assessment, since these might alter the results. For example, it is relevant to evaluate cognitive deficits in order to judge whether the patient can reliably answer a self-report questionnaire or whether it is better to obtain the information through other means (e.g. interview). Indeed, those with attention deficits or with difficulties with abstract concepts can struggle with choosing an answer on a scale, such as Likert scales, especially if the proposed answers offer subtle differences.

Assessments in mental health typically involve ordinal scales, also known as Likert scales, where a concept is measured, for example, from 1 = not present to 7 = extremely severe. Other scales are dichotomous (1 = yes, 2 = no), continuous (rate from 1 to 100), or use specific intervals or anchor points. The two most important aspects to consider before using rating scales are the context in which the evaluation has to be undertaken, whether it be for assessing needs, skills, change over time, etc.; and the psychometric qualities of the scale, i.e. its reliability and validity. Reliability is the ability of the scale to

convey consistent and reproducible information. Validity is the degree to which the scale measures what it is supposed to measure in an exact manner¹.

This chapter provides clinicians with an overview of selected rating scales that can be used to help monitor and assess patients with schizophrenia, in terms of clinical and broader psychosocial parameters. The selection criteria adopted are outlined in Box 17.1.

Rating scales assessing symptoms, needs, strengths, skills, and deficits

Tools presented in this section aim at assessing clients' symptoms, needs, strengths, skills, and deficits in order to offer them the most appropriate services. These scales can be used in a multidisciplinary team context to better understand the clients and help them meet their goals.

Symptoms

There exist various scales specifically designed to assess symptoms in individuals with schizophrenia. For example, the Brief Psychiatric Rating Scale (BPRS)² and the Positive and Negative Symptom Scale (PANSS)³ are widely used. Other

Box 17.1 Criteria for selection of rating scales.

- Utility in clinical practice – many other measures exist and some are more relevant for research purposes
- The most important needs, deficits, symptoms, and patient profiles linked to recovery are covered
- Easy to administer – none of the measures necessitate specific training or lengthy manuals
- Brief – length of assessment was considered
- Easily accessible, with low or no payment required for use
- Demonstrated adequate psychometric qualities with individuals with schizophrenia
- Some of the instruments can be used at various points in time to measure change, if that is the goal
- Some of the instruments generate various subscales as well as more general score(s) that are easy to calculate and interpret
- Some of the instruments are self-report, others are informant or clinician-report and others have both versions available

assessments aim at measuring more specific sets of symptoms such as the psychotic symptom rating scales (PSYRATS) for hallucinations and delusions⁴, the scale for the assessment of positive symptoms (SAPS) for positive symptoms, and the scale for the assessment of negative symptoms (SANS) for negative symptoms⁵. However, all of these measures necessitate specific training, usually involving inter-rater reliability checks, videotape ratings, and regular supervision. Since we only wish to present measures that do not require extensive training, we will not describe the above-mentioned instruments, though they can be clinically useful to assess the impact of medication or other treatments when clinicians are properly trained in administering them.

Brief Symptom Inventory

Description The Brief Symptom Inventory (BSI)⁶ is a shortened version of the SCL-90 (Symptom Check List-90), and consists of 53 items to assess psychological distress and symptom severity in both patient and non-patient populations. The BSI measures the experience of symptoms in the previous 7 days, and consists of nine scales: Somatization, Obsessive-compulsive, Sensibility, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation, and Psychoticism; and three additional scales to measure global symptom severity, positive symptom distress, and positive symptoms. Psychologists, psychiatrists, physicians, nurses, and other health-care professionals can use the BSI instrument to assess individuals at intake for psychological problems and measure their progress following a treatment (for more details, see Table 17.1).

Scoring Items are rated on a five-point rating scale from 0 (no at all) to 4 (extremely). In addition to the nine symptom dimensions, three global indices assess a patient's general psychiatric distress: Global Severity Index (GSI), Positive Symptom Distress Index (PSDI), and Positive Symptom Total (PST). For example, the GSI was conceived to quantify a patient's severity-of-illness or symptom severity. Scores for each subscale are between 0 and 4. There are established norms for various clinical groups, including adult psychiatric outpatient or adult psychiatric inpatient populations.

The Behaviour and Symptom Identification Scale

Description The Behaviour and Symptom Identification Scale (BASIS-32)⁷ measures symptoms and social functioning with 32 items, which are spread out in five subscales: Psychosis, Impulsivity and Addictive Behavior,

Table 17.1 Rating scales in schizophrenia

	<i>What it measures</i>	<i>Type of measure</i>	<i>Length of administration</i>	<i>Advantages</i>	<i>Inconveniences</i>
BSI ⁶	Psychiatric symptoms	Self-rated	15–20 minutes	Assesses various symptoms, not only linked to schizophrenia	Self-report only, some information might need to be obtained through more detailed interview or chart
BASIS-32 ⁷	Symptoms and functioning	Self-rated	15–30 minutes	Validated in multiple countries, with large samples – many norms exist	Not suggested for individual clinical decisions. Scales are statistically derived – not always easy to interpret clinically
CDSS ⁸	Depressive symptoms	Interview	20–30 minutes	Adapted for schizophrenia, truly measures depression and not positive or negative symptoms, or extrapyramidal side-effects of medication. Available in multiple languages	Only one global score, only one version (interview based)
CAN ⁹	Community functioning needs	Self-rated and clinician-rated	15–60 minutes	Covers many domains. Has two versions and adaptations according to age group. Available in many languages and has many norms	Not in depth, each domain is briefly covered

CASIG ³⁰	Community functioning, goals, needs, quality of life, and more	Self-report (CASIG-SR) and Informant version (CASIG-I)	60 minutes for the CASIG-SR and 45 minutes for the CASIG-I	Covers many areas. Includes two versions. In depth, useful for planning treatment with clients. Available in paper and CD-rom	Assessments are long. Questions are mostly dichotomous
MMLT ¹²	Readiness for skills training	Interactive, video, questions & role-plays	35–50 minutes	Good screening for cognitive difficulties that on benefiting from skills training. A different version exists for each skills training module	Only linked to the might impede UCLA skills modules. Necessitates equipment (VHS)
SFS ¹⁴	Social competence	Semi-structured interview, and version for family members	20–30 minutes for each version	Two versions Covers many aspects	Different rating scales and anchor points – can be a bit confusing to score
WBI ¹⁵	Vocational functioning	Observational measure that includes employer/supervisor interview	15 minutes behavioral observation plus a brief interview with employer or supervisor	Real-life observations in work settings of the client	Can only be used if employer is aware of the mental condition
SES ¹⁹	Engagement in services	Clinician report	10–5 minutes	Helps determine profiles of treatment adherence and engagement with services	Only one version – no information is obtained on reasons for difficulties with engagement

Continued

Table 17.1 Rating scales in schizophrenia—cont'd

	<i>What it measures</i>	<i>Type of measure</i>	<i>Length of administration</i>	<i>Advantages</i>	<i>Inconveniences</i>
SERS-SF ²⁰	Self-esteem	Self-rated	15–20 minutes	Many aspects of self-esteem are measured, including positive and negative self-esteem. More adapted to schizophrenia and more specific than other measures (i.e. Rosenberg Self-Esteem Scale)	The scoring involves negative scores, at times difficult to interpret
TLFBC ²³	Substance abuse	Interview	Varies according to addiction patterns – from 10 to 30 minutes	More accurate than most self-report addiction measures. Accurate profile of use	Does not give scores or norms. Does not determine diagnosis of dependence or abuse
MADS ²⁴	Delusions	Interview	20–45 minutes	In depth. Useful for determining the impact of delusions on person's life	Different scoring for the subscales – can be tedious

BAVQ-R ²⁵	Auditory hallucinations	Self-rated	15–20 minutes	Covers various dimensions of voices, and the impact on the person's life	Does not address form or content of hallucinations
WAI ²⁶	Working alliance	Self-rated (client and clinician version)	10 minutes	Two versions of the relationship between the client and clinician. Many versions exist (short, long, with or without subscales)	High correlations between subscales
SLDS ²⁹	Quality of life	Self-rated	10–20 minutes	Can be used with individuals with cognitive deficits, because of scale using smiling frowning faces. Many domains covered	Not in depth, each domain is briefly covered

BSI: Brief Symptom Inventory; BASIS: The Behaviour and Symptom Identification Scale; CDSS: The Calgary Depression Scale; CANI: The Camberwell Assessment of Needs; CASIG: Client Assessment of Strengths Interests and Goals; MMLT: Micro-Modules Learning Test; SFS: Social Functioning Scale; WBI: Work Behavior Inventory; SES: Service Engagement Scale; SERS-SF: Self-Esteem Rating Scale- Short-Form; TLFBC: Drug/Alcohol Time Line Follow-Back Calendar; MADS: MacArthur-Maudsley Delusions Assessment Schedule; BAVQ-R: Belief about Voices Questionnaire-Revised; WAI: The Working Alliance Inventory; SLDS: Satisfaction with Life Domains Scale.

Anxiety/Depression, Interpersonal Relations, and Living Skills and Role Functioning. The scale measures the degree of difficulty the person has experienced in the last 7 days for each item. Since only the past week is assessed, it can also be used at regular intervals to assess change over time, for example, before and after receiving care. The BASIS-32 is more often used for assessing large groups of clients and determining their clinical and social functioning than for specific treatment purposes.

Scoring Scoring the 32 items provides summary indicators of how individuals feel on domains of psychiatric, substance abuse symptoms, and functioning. The BASIS-32 measures the degree of difficulty experienced by the individual on a five-point scale ranging from 0 = no difficulty to 5 = extreme difficulty. The BASIS-32 is scored using an algorithm that gives an overall score with the five subscales mentioned above.

The Calgary Depression Scale

Description The Calgary Depression Scale for Schizophrenia (CDSS)⁸ is a nine-item scale specifically developed for the assessment of depression in schizophrenia patients. It is a semistructured goal-directed interview assessing depression, hopelessness, self-depreciation, guilty ideas of reference, pathological guilt, morning depression, early waking, suicide, and observed depression during the interview.

Scoring The CDSS is a semistructured interview with specific questions and probes for each of the nine items, rated from 0 (absent) to 3 (severe). A total score is obtained by adding each of the item scores. Norms and cut-off points are available.

Needs and strengths

With services aiming at helping individuals in their recovery process, patients' goals, needs, and strengths are central aspects of the treatment. Qualitative interviews can also serve this purpose but might result in omissions in questioning on certain central aspects of their experience, such as spiritual goals, sexual problems, or needing help with raising the children. The following measures either cover many domains or cover particular areas in a fairly comprehensive manner.

The Camberwell Assessment of Needs

Description The Camberwell Assessment of Needs (CAN)⁹ measures the level of difficulty and level of assistance needed in the previous month, for people with mental health problems. It covers 22 areas of functioning including

housing, food, cleaning, hygiene, daily activities, physical health, psychotic symptoms, treatment or illness information, psychological distress, personal security, social security, security of others, alcohol, drugs, social relationships, emotional relationships, sexual life, care of children, education, financial tasks, use of the telephone, and use of public transportation.

Scoring The patient and his/her clinician independently rate both the patient's difficulties in functioning and the assistance provided to them in each of the 22 areas (essentially one question per area). The need rating for each area is as follows: 'no need' (score of 0) – they have no serious problems in the area; 'met need' (score of 1) – they have no or moderate problems in the area due to help given; 'unmet need' (score of 2) – a serious problem, irrespective of any help given; and 'not known' (no score or missing score) – either not known or not disclosed. Also, when a met or unmet need is identified, further questions are asked to identify how much help the individual is receiving from informal sources (e.g. relatives) and formal sources (e.g. community services), and how much help they need from formal sources.

Client Assessment of Strengths, Interests, and Goals

Description The Client Assessment of Strengths, Interests, and Goals (CASIG)¹⁰ is a comprehensive functioning assessment which addresses most psychiatric rehabilitation treatment domains, namely community living skills, cognitive skills, medication practices (compliance and side-effects), quality of life, quality of treatment, symptoms, consumer rights, and unacceptable community behaviors. Each scale ends with a goal question pertaining to that domain. The community living skills and symptom domains are adapted from the Independent Living Skills Survey (ILSS)¹¹ and the BPRS², respectively. The assessment also elicits goals in five broad areas (residence, financial, relationships, religion/spirituality, and physical and mental health). The CASIG assesses multiple outcomes that focus on strengths and skills. It is capable of assessing change over time (can be re-administered every 3 months).

Scoring The domain related to the 'goals' is addressed by open-questions while all the other sections, including the community living skills, medication practices, side-effects, symptoms, cognitive difficulties, consumer rights, quality of life, quality of treatment, and unacceptable community behaviors, are built with dichotomous questions (yes/no) and can be added up for each subscale (yes = 1, no = 0). Following each domain, or subscale, a yes/no question is asked to determine whether the client wishes to make that domain a personal goal. If yes, a four-point Likert scale (from 'none' to 'a lot') follows to assess how much help the client believes he/she needs to meet that goal.

Skills and deficits

Various instruments assess skills and deficits, with some comprehensive measures incorporating a number of such scales (for example, the CASIG includes most of the ILSS items). Deficits, especially cognitive deficits, are typically assessed with cognitive tests by trained neuropsychologists, but can also be assessed indirectly through novel techniques. Here we present scales covering only three essential domains of skills and deficits, i.e. social skills training readiness/cognitive deficits, social functioning, and work competence.

Micro-Modules Learning Test

Description The Micro-Modules Learning Test (MMLT)¹² is a measure of three major components of skills training: responsiveness to verbal instructions, ability to learn from watching a modeled behavior, and ability to reproduce behavior in a role-play. Contrary to the Assessment of Interpersonal Problem Solving Skills (AIPSS)¹³, which focuses mostly on problem solving social situations, the MMLT comes in different versions in order to apply them to any of the UCLA social skills training modules (see Chapter 11), and does not necessitate any training. It also is highly correlated with measures of cognition, particularly verbal memory and verbal fluency, as well as theory of mind, suggesting that individuals who score poorly on the MMLT could benefit from cognitive remediation prior to taking part in a skills training group (see also Chapter 4).

Scoring The MMLT comes with verbal instructions, written instructions, a videotape, and a scoring sheet with specific anchor points. Each question contains three levels of difficulty and the participant is rated according to the level achieved (0 if all wrong, to 3 if the most difficult level was correct).

Social Functioning Scale

Description The Social Functioning Scale (SFS)¹⁴ is a 79-item scale that assesses social functioning and more particularly abilities and performance of people with schizophrenia in seven areas: withdrawal/social engagement, interpersonal communication, independence-performance, independence-competence, recreation, prosocial, and employment/occupation.

Scoring A scoring algorithm is provided for each scale and allows the identification of specific problem areas. Each scale is rated in various ways (Likert scales, ratings from 0 to 100, yes/no answers, straight answers (e.g. number of friends)). It covers in detail many aspects of social competence and is designed to assess change over time, particularly following clinical interventions such as family therapy.

Work Behavior Inventory

Description The Work Behavior Inventory (WBI)^{15,16} is a 36-item vocational situational assessment used to measure work function/performance for people with severe mental illness with the following five subscales: Work Habits, Work Quality, Personal Presentation, Cooperativeness, and Social Skills. Items stem from other measures of work behavior such the Work Personality Profile (WPP)¹⁷ and the Minnesota Satisfactoriness Scales (MSS)¹⁸, and from additional observations and supervision at work sites. The WBI can be very useful for job coaches or vocational rehabilitation specialists wishing to offer precise and useful support to their clients who are working (see also Chapter 12).

Scoring The items are assessed on a five-point anchorage with behavioral examples, from 1 to 5, 1 representing consistently inferior performance, 5 representing consistently superior performance, and 2, 3, and 4 representing intermediate points on the performance continuum. Each continuum combines frequency and severity of problem behaviors. Each of the five subscales contain seven items and the final item is a global item reflecting overall work performance. The WBI subscales range from 7 to 35, and the summation of all scores gives the total score.

Specific mediators and moderators

Even though symptoms, needs, skills, and strengths are important aspects to measure before, during, and after a treatment, other crucial variables or specific mediators and moderators can also be assessed when wishing to better understand the individual's situation or in order to insure that the treatment is as effective as possible. Such mediators and moderators, when problematic, often become treatment targets. For instance, treatment outcome is directly influenced by treatment adherence, which can be influenced by the relationship between the client and the therapist, as well as by other factors such as the patient's substance use, self-esteem, and quality of life. Another example is that the individual's symptoms might have decreased with the appropriate medication but specific beliefs continue to cause distress and might necessitate a specific treatment, such as cognitive behavior therapy (see Chapter 2).

Service Engagement Scale

Description The Service Engagement Scale (SES)¹⁹ is a 14-item measure consisting of statements that assess patient's engagement with services.

Scoring Items are assessed on a four-point Likert scale from ‘not at all or rarely’ to ‘most of the time’. The total score ranges from a minimum of zero to a maximum of 42. Higher scores indicate lower engagement. Four subscales assess availability (‘When a visit is arranged, the client is available’), collaboration (‘The client actively participates in managing his/her illness’), help-seeking (‘The client seeks help to prevent a crisis’), and treatment adherence (‘The client refuses to cooperate with treatment’).

Self-Esteem Rating Scale-Short Form

Description The Self-Esteem Rating Scale-Short Form (SERS-SF)²⁰ is an abbreviated version of the SERS²¹ and involves statements that are linked to social contacts, such as friends, as well as achievements and competency. The SERS-SF consists of two scales, positive and negative self-esteem, which have been documented as being relevant for individuals with schizophrenia^{20,22}. The SERS-SF taps into multiple aspects of self-evaluation such as overall self-worth, social competence, problem-solving ability, intellectual ability, self-competence, and worth compared to others.

Scoring The items are rated on a seven-point Likert scale (from 1 = never to 7 = always), ten scored positively and ten negatively, with scores ranging from –70 to –10 (negative items) and from 10 to 70 (positive items). Both the exploratory and confirmatory factor analyses have found that the 20-item SERS-SF has high validity, and is, in fact, superior in terms of construct validity and parsimony to the original 40-item SERS²⁰.

Drug/Alcohol Time Line Follow-back Calendar

Description Compared with other lengthy addiction self-report instruments that mostly aim at determining a diagnosis of dependence or abuse (e.g. the Addiction Severity Index, the Alcohol Use Scale, and the Drug Use Scale) the most clinically useful addiction instrument is probably the Drug/Alcohol Time Line Follow-Back Calendar (TLFBC)²³. The TLFBC provides a summary of the client’s use of substances over the past 6 months, has a high accuracy rate, and can help clinicians determine patterns of abuse and change over time.

Scoring The TLFBC is conceived as a grid that helps go back in time, a month at a time, to determine what the person used, the frequency of use within the month, and the quantities used for each day.

MacArthur-Maudsley Delusions Assessment Schedule

Description The MacArthur-Maudsley Delusions Assessment Schedule (MADS)²⁴ consists of seven dimensions: conviction, negative affect, action,

inaction, preoccupation, pervasiveness, and fluidity. The Conviction subscale represents subjects' certainty about the delusional belief; the Negative Affect subscale addresses whether the delusional belief makes subjects unhappy, frightened, anxious, or angry; the Action subscale is the extent to which subjects' actions are motivated by the delusional belief; the Inaction subscale is whether subjects have refrained from any actions (e.g. eating, drinking) because of the delusional belief within the previous 2 months and since the delusions began; the Preoccupation subscale assesses the extent to which the subjects indicate that their thoughts focus exclusively on the delusion; the Pervasiveness subscale reflects the degree to which the delusional belief penetrates all aspects of the subjects' experiences; and the Fluidity subscale the degree to which the delusional belief changed frequently during the interview, often encompassing new people or contexts as they entered the discussion.

Scoring Specific questions are asked about the first four dimensions; the last three are rated on anchored scales on the basis of the interviewers' global impressions. The summation of the four Conviction items varies from 0 to 8, the summation of the four Negative Affect items ranges from 0 to 4. With respect to the Actions subscale, the 13 questions are either specific or open-ended. The Inaction subscale comprises eight questions (score from 0 to 8). Preoccupation and Pervasiveness subscales are one item with either a score from 0 to 3 or a score from 0 to 4, respectively. Finally, the fluidity subscale varies from no variation (score of 0) to frequent changes (score of 2).

Belief About Voices Questionnaire-Revised

Description The Belief about Voices Questionnaire-Revised (BAVQ-R)²⁵ consists of 35 items assessing people's beliefs about their auditory hallucinations, as well as their emotional and behavioral reactions to them. Three subscales measure beliefs about the voice, i.e. its intent on doing good (benevolence, six items) or on harming (malevolence, six items), and its power (omnipotence, six items). Two further subscales, 'resistance' (nine items) and 'engagement' (eight items), measure how the person reacts emotionally and behaviorally to his/her voices).

Scoring All the items are rated on a four-point scale ranging from disagree (0) to agree strongly (3). Scores are added according to each of the five subscales mentioned above.

The Working Alliance Inventory

Description The Working Alliance Inventory (WAI)²⁴ is a self-administered questionnaire and reflects the quality of the client and patient's therapeutic

relationship. There are three subscales: the Bond subscale reflects the positive relationship between the therapist and the client. The Task subscale concerns the behaviors and cognitions that support the agreement between the therapist and the client on the tasks to be accomplished. The Goal subscale concerns the collaboration between the therapist and the client regarding the goals to be attained.

Scoring The WAI authors recommended that four scores be considered, one from each of the three subscales (i.e. Bond, Task, and Goal), and one overall score²⁶. The global scale simply represents the sum of all items. All items are assessed on a seven-point Likert-type scale (from 1 = never to 7 = always). The authors initially built the scale with 36 items, holding three 12-item subscale scores – Bond, Task and Goal – as well as one overall score. Subsequently, Tracey and Kokotovic²⁷ proposed a short-form scale containing 12 items drawn in equal proportion from the three initial subscales. Even though the Bond, Task, and Goal subscales are distinct components of the WAI, they remain strongly intercorrelated at empirical and statistical levels for people with severe mental illness²⁸.

Satisfaction with Life Domains Scale

Description The Satisfaction with Life Domains Scale (SLDS)²⁹ comprises 15 life domains: housing, neighborhood, food, clothing, health, room-mate, friends, relationship with family, getting on with other people, job or day programming, activity in spare time, activity for fun, services in the area, economic situation, and living place in comparison with state hospital. Other versions with more items have been developed for specific purposes (e.g. breast cancer).

Scoring Respondents use a seven-point Likert scale to rate the items. They are asked to indicate their feelings by choosing one of seven faces, gradually changing from a ‘delighted’ face with a large upturned smile (scored 7) to a ‘terrible’ face with a deep frown (scored 1) – thus making the assessment easy to answer for most people.

Conclusions

This chapter provides a selected overview of rating scales that clinicians might use in their practice when working with individuals with schizophrenia. Since many different scales and types of measures exist, we recommend choosing measures that are validated and appropriate for the setting and clientele. The measures proposed here were all selected according to these

criteria, as well as others such as necessitating no specific training and being quick and easy to administer. Some of the measures have been used for many years and have ample empirical support, whereas others are more recent. Many other measures could have been presented since the list is not exhaustive.

Individuals with schizophrenia rarely follow a linear path in terms of recovery; rating scales can help them as well as the clinicians gain a better understanding of these changes over time and the potential effects of the treatments or services received. Rating scales can be used at various times during treatment or the recovery process, either to help gain knowledge and build a working alliance, or to evaluate progress and change, or even to determine the effectiveness of specific services offered by a mental health team. Last but not least, clinical rating scales can help create bridges between research and clinical practice and potentially initiate fruitful collaborations that can help improve services and the recovery process of individuals with schizophrenia.

References

1. Anastasi A. *Psychological Testing*. New York: Macmillan, 1988.
2. Lukoff D, Nuechterlein KH, Ventura J. Manual for expanded brief psychiatric rating scale. *Schizophr Bull* 1986; 12: 594–602.
3. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; 13: 261–76.
4. Haddock G, McCarron J, Tarrier N et al. Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychol Med* 1999; 29: 879–98.
5. Andreasen NC, Olsen S. Negative vs positive schizophrenia: definition and validation. *Arch Gen Psychiatry* 1982; 39: 784–94.
6. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med* 1983; 13: 596–605.
7. Eisen SV, Dill DL, Grob MC. Reliability and validity of a brief patient-report instrument for psychiatric outcome evaluation. *Hosp Community Psychiatry* 1994; 45: 242–7.
8. Addington D, Addington J, Maticka-Tyndale E et al. Reliability and validity of a depression rating scale for schizophrenics. *Schizophr Res* 1992; 6: 201–8.
9. Phelan M, Slade M, Thornicroft G et al. The Camberwell assessment of need: the validity and reliability of an instrument to assess the needs of people with severe mental illness. *Br J Psychiatry* 1995; 167: 589–95.
10. Wallace CJ, Lecomte T, Wilde J, Liberman RP. CASIG: a consumer-centered assessment for planning individualized treatment and evaluating program outcomes. *Schizophr Res* 2001; 50: 105–9.
11. Wallace CJ, Liberman RP, Tavber R, Wallace J. The independent living skills survey: a comprehensive measure of the community functioning of severely and persistently mentally ill individuals. *Schizophr Bull* 2000; 26: 631–58.

12. Silverstein SM, Wallace CJ, Schenkel LS. The micro-module learning tests: work-sample assessments of responsiveness to skills training. *Schizophr Bull* 2005; 31: 73–83.
13. Donahoe CP, Carer MJ, Bloem WD et al. Assessment of interpersonal problem solving skills. *Psychiatry* 1990; 53: 329–39.
14. Birchwood M, Smith J, Cochrane R et al. The social functioning scale: the development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. *Br J Psychiatry* 1990; 157: 853–9.
15. Bryson G, Bell MD, Lysaker P et al. The Work Behavior Inventory: a scale for the assessment of work behavior for people with severe mental illness. *Psychiatr Rehabil J* 1997; 20 (Suppl 4): 47–55.
16. Lysaker P, Bell M, Bryson G et al. Raters guide for the work behavior inventory: rehabilitation, research, and development service. West Haven, CT: Department of Veteran Affairs, 1993.
17. Bolton B, Roessler R. Manual for the Work Personality Profile. Fayetteville, AR: University of Arkansas Research & Training Center in Vocational Rehabilitation, 1986.
18. Gibson DL, Weiss DJ, Dawis RV et al. Manual for the Minnesota Satisfactoriness Scales. Minneapolis, MN: University of Minnesota, 1977.
19. Tait L, Birchwood M, Trower P. A new scale (SES) to measure engagement with community mental health services. *J Ment Health* 2002; 11: 191–8.
20. Lecomte T, Corbière M, Laisné F. Investigating self-esteem in individuals with schizophrenia: relevance of the self-esteem rating scale-short form. *Psychiatry Res* 2006; 143: 99–108.
21. Nugent WR, Thomas JW. Validation of a clinical measure of self-esteem. *Res Soc Work Pract* 1993; 3 (Suppl 2): 191–207.
22. Barrowclough C, Tarrier N, Humphreys L et al. Self-esteem in schizophrenia: relationships between self-evaluation, family attitudes, and symptomatology. *J Abnorm Psychol* 2003; 112 (Suppl 1): 92–9.
23. Mueser KT, Noordsy DL, Drake RE et al. Integrated treatment for dual disorders: a guide to effective practice. New York: Guilford Press, 2003.
24. Taylor PJ, Garety P, Buchanan A et al. Delusions and violence, in violence and mental disorder: developments in risk assessment. Chicago, IL: University of Chicago Press, 1994.
25. Chadwick P, Lees S, Birchwood M. The revised beliefs about voices questionnaire (BAVQ-R). *Br J Psychiatry* 2000; 177: 229–32.
26. Horvath AO, Greenberg LS. Development and validation of the working alliance inventory. *J Coun Psychology* 1989; 36 (Suppl 2): 223–33.
27. Tracey TJ, Kokotovic AM. Factor structure of the working alliance inventory. *Psychol Assess* 1989; 1 (Suppl 3): 207–10.
28. Corbière M, Bisson J, Lauzon S et al. Factorial validation of a French short-form of the working alliance inventory. *Int J Meth Psychiatr Res* 2006; 15 (Suppl 1): 36–45.
29. Baker F, Intagliata J. Quality of life in the evaluation of community support systems. *Eval Program Plann* 1982; 5: 69–79.
30. Wallace CJ, Liberman RP, Tauber R, Wallace J. The independent living skills survey: a comprehensive measure of the community functioning of severely and persistently mentally ill individuals. *Schizophr Bull* 2000; 26: 631–58.

Index

Page references in *italics* refer to figures and tables.

- acamprosate 107
- acute arousal:
 - atypical antipsychotics dosage 118
 - see also* acute behavioral disturbance
- acute arousal scale 113–14, 114
- acute behavioral disturbance 111–25
 - atypical antipsychotics 117–21, 118
 - first-episode schizophrenia 212
 - non-pharmacological strategies 114–17
 - organic causes 111–12
 - pharmacological strategies 117–25
- algorithmic approach 119–21, 120
 - predictors of aggression 113–14, 113–14
 - in psychosis 112
 - typical antipsychotics 117
- acute dystonic reaction 19
- Adams, C.E. 16
- adherence, treatment 7, 102, 143–9, 247
 - depot antipsychotics 16–18
 - enhancing 149
 - factors affecting 143–6, 144
 - first-episode schizophrenia 214–15
 - promoting 146–9
 - treatment-resistant schizophrenia 228
- agitation 19
- agitation and arousal medication chart 122
- agranulocytosis 1
- akathisia 1, 2, 19, 36, 63, 65, 117
- akinesia 63, 65
- alcohol abuse 88, 100
- alogia 35
- alprazolam 137
- alternative therapies 23–32
- amisulpride 2, 5, 6, 8, 9, 39
- acute behavioral disturbance 117–18
 - in augmentation 15
 - use with clozapine 12
 - and delirium 112
 - in early episode psychosis treatment 7
 - amphetamines 101
 - acute behavioral disturbance (*Continued*)
- Andreasen, N.C. 63
- anhedonia 35, 61
- anti-epileptic drugs 137
- anticholinergics 39, 107
- antidepressants:
 - use with antipsychotics 66–7
 - in augmentation 13, 15
 - first-episode schizophrenia 216
 - and substance abuse 107
- antipsychotics 1–20
 - with antidepressants 13, 66–7
 - in combination 12
 - complications 18, 19, 19
 - and delirium 112
 - and depression 63, 64
 - dosages 38–9, 182, 210, 211
 - dyslipidemia 86
 - and estrogen 181–2
 - extrapyramidal side-effects (EPSE) 2, 38–9
 - first-episode schizophrenia 209–10
 - and hyperglycemia 87
 - and insulin resistance 87
 - and metabolic syndrome 88
 - negative symptoms 36, 36, 38–40
 - reducing violence 137
 - relapse 214–15
 - second generation drugs 38, 211
 - and selective serotonin reuptake inhibitors (SSRIs) 67
 - and ‘self medication’ 107
 - and sexual functioning 184
 - switching 15–16, 17
 - treatment-resistant schizophrenia 221–3
 - treatment response of women 182
 - and weight gain 85–6
 - women 182, 184–5, 186, 187, 187–8
 - see also* atypical antipsychotics; typical antipsychotics; specific drugs

- antisocial behavior 129, 131–2
- anxiety disorders 67–74, 69
- first-episode schizophrenia 215–16
 - and voices 24, 25, 26
- apolipoprotein E 15
- Arango, C. 117
- aripiprazole 2–3, 5, 6, 8, 9, 38, 211
- acute behavioral disturbance 117–18, 118
 - use with clozapine 13
 - and delirium 112
 - and metabolic syndrome 88
 - treatment-resistant schizophrenia 221–3
 - and weight 85, 86
- arousal *see* acute arousal; acute behavioral disturbance
- asenapine 3
- assertive community treatment 227
- Assessment of Interpersonal Problem Solving Skills (AIPSS) 246
- atypical antipsychotics 1, 2, 5, 7, 8, 10
- acute agitation 212
- acute arousal and agitation in psychosis 118, 120
- acute behavioral disturbance 117–21
- antidepressant effects 64
- and cognitive dysfunctions 52–3
- and delirium 112
 - depot formulations 16–18
 - use in depression 66
 - and dyslipidemia 86
 - first-episode schizophrenia 210–12
 - long-acting 18
 - and menstrual cycle 184
 - and obsessive compulsive symptoms 74
 - primary negative symptoms 39–40
 - second generation 38, 39–40, 211
 - side-effects 5, 6
 - and social competence 71
 - and substance abuse 107, 107
 - treatment-resistant schizophrenia 224–5
 - and typical agents 12
 - and weight gain 85, 85–6
 - see also* specific drugs
- auditory hallucinations 24–27
- augmentation strategies 12–15, 15

- Baker, R.W. 117
- Barrowclough, C. 106, 195
- Bayle, F.J. 67
- Behavior and Symptom Identification Scale (BASIS-32) 239, 240, 244
- behavior management programs (BMPs) 227, 230
- behavioral disturbance, acute *see* acute behavioral disturbance
- Belief About Voices Questionnaire-Revised (BAVQ-R) 243, 249–250
- Bell, M. 54
- Bellack, A.S. 167
- benperidol 4
- bentropine 111
- benzamides, substituted 4
- benzodiazepines 111, 119, 212
 - acute arousal and agitation in psychosis 120
 - in acute behavioral disturbance 119, 121
 - in augmentation 15
 - and delirium 112
 - reducing violence 137
 - and substance abuse 107
- benzotropine 39
- Bernado, M. 117
- bifeprunox 3
- Birchwood, M. 26
- Bleuler, E. 47, 61
- blunted affect 42
- body mass index 91
- Bottas, A. 73
- bradykinesia 36
- Braga, R.J. 68
- breast cancer 186
- Brief Psychiatric Rating Scale (BPRS) 230, 245
- Brief Symptom Inventory (BSI) 239, 240
- bromocriptine 18
- Brown, S. 82
- Buckley, P.F. 67
- butyrophenones 4

- caffeine abuse 99
- Calgary Depression Scale for Schizophrenia (CDSS) 240, 244
- Camberwell Assessment of Needs (CAN) 240, 244–5
- cancer 82, 83–4
- cannabis 100, 101
- Cannon, M. 48
- Canto-Graae, E. 100
- carbamazepine:
 - in augmentation 13, 15
 - contraindication with clozapine 13
 - in reducing violence 137
- cardiovascular disease 82, 82–3, 186, 187, 187
- Casey, D. 188
- Cassano, G.B. 67
- Castle, D.J. 68
- catatonia 36, 37
- cerebrovascular disease 82
- Chadwick, P. 26
- Chaves, M.P.R. 74
- chlorpromazine 1, 4, 38, 111
 - acute arousal and agitation in psychosis 120
 - and delirium 112
- first-episode schizophrenia 210–11
- cholinergic rebound 17
- circulatory disease 82
- Clements, K. 194
- Client Assessment of Strengths, Interests, and Goals (CASIG) 241, 245–6
- Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) 10, 82, 86, 87–88
- clinical assessment 206–10, 207–8, 213–14
- clomipramine 74

- clonazepam:
 - acute arousal and agitation in psychosis 120
 - acute behavioral disturbances 119
 - reducing violence 137
- Clopixol Acuphase *see* zuclopenthixol
- clozapine 1–2, 5, 6, 8, 9, 10–12, 66
 - augmentation 12–13, 15
 - cognition, effects on 52
 - early episode psychosis treatment 7
 - first-episode schizophrenia 210–11, 215
 - negative symptoms 36, 39, 41
 - obsessive compulsive symptoms 74
 - reducing violence 137
 - and ‘self medication’ 107, 107
 - side-effects 1–2, 10, 12
 - social anxiety disorder 71
 - treatment flow chart 11
 - treatment-resistant schizophrenia 221, 225
- cocaine 101
- cognition:
 - women 180–2
- social: interventions 172, 173
 - cognitive adaptional training 57–8
- cognitive behavior therapy (CBT) 28–31
 - and adherence 146–9
- first-episode schizophrenia 213
- groups 31
 - hallucinations 27
 - negative symptoms 41
 - outcomes 30–1
 - social anxiety disorder 70–1
 - treatment-resistant schizophrenia 226, 228–9
 - trials 30–1
 - and work 154–7
- cognitive dysfunction 47–58
- cognitive deficits 47–9, 49
- effect on life skills 51
 - pharmacological approaches 52–3
 - psychological approaches 53–58
 - rehabilitation 50–1
 - treatment issues 51–2
- cognitive enhancement therapy (CET) 226
- cognitive intervention: voices 25
- cognitive remediation: work 158–61
- cognitive remediation therapy (CRT) 54–7, 55, 56
- communication: social skills training 167
- Community Support Program (CSP) 104–5
- comorbidities 67–9, 72–3
 - women 180
- competency 231, 231,
- compliance *see* adherence, treatment
- concordance *see* adherence, treatment
- Corrigan, V.A. 201
- Cosoff, S.J. 67, 68, 70
- criminal behavior 102, 130–1
- Cuffel, B.J. 102

- D-cyloserine 40
- D2 antagonists 224
- D2 blockers 1, 3, 15

- dantrolene 18
- delirium 111–12
- delusions:
 - and adherence 144
 - psychological interventions 27–28
 - and violence 132
- depot antipsychotics 16–18
 - relative side-effects 14
- deprenyl 40
- depression 19, 36–7, 39, 61–7, 62
 - and antipsychotic drugs 64
 - effect on schizophrenia 62–3
 - factors to exclude 65
 - first-episode schizophrenia 215–16
 - pharmacological approaches 66
 - psychological approaches 65–6
 - recognizing 63, 63
 - treatment 65–7
- diabetes mellitus 82, 83, 91, 186, 211
 - screening 90, 92
- diagnosis:
 - first-episode schizophrenia 205–10, 207–8
 - negative symptoms 36, 36–7
 - treatment-resistant schizophrenia 222
- diazepam 120
- dibenzodiazepines 5
- dibenzoxazepine 4
- diphenylbutylpiperidine 4
- disulfiram 107
- dopamine 1, 2–3
 - effect of estrogen on 181
 - receptors 38, 107
- dosages 4, 6, 38–9
 - acute arousal 118, 121
 - atypical antipsychotics 5
 - effect on cognition 52–3
 - first-episode schizophrenia 210–11
 - treatment-resistant schizophrenia 224–5
 - women 182, 185
 - Drake, R.E. 104, 105
- droperidol 3, 117
- Druss, B.G. 88
- Dufresne, R.L. 67
- duration of untreated psychosis (DUP) 205–6, 216–17
- dyslipidemia 85, 86, 88
- dysphoria 65
- dystonias 1, 2, 117, 211
 - in women 187–8

- early episode psychosis 7, 8
- see also* first episode schizophrenia
- Eisen, J.L. 72
- electroconvulsive therapy (ECT) 13, 67, 74
- Emsley, R.A. 64
- endocrine diseases 82
- enduring symptoms 35
- environmental effects 40–1, 57–8, 226–7
- Epidemiology Catchment Area Survey (ECA) 100
- epilepsy 82

- Escher, S. 27
 estradiol 181
 estrogen 180–2
 augmentation 181
 exposure and response prevention (ERP) 73
 expressed emotion (EE) 194, 200
 extrapyramidal side-effects (EPSE) 1, 2, 3, 4, 7, 10
 and cognitive dysfunctions 52
 first-episode schizophrenia 210, 211
 acute behavioral disturbance 117
 minimizing 38
 and negative symptoms 36, 36, 38
 women 187–8
- Fabisch, K. 72–4
 Falloon, I.R.H. 196, 197
 family intervention 193–201
 background to 193–4
 dissemination 200–1
 first-episode schizophrenia 212–13
 results of studies 196–200, 197–9
 studies 194–200, 197–9
- Fenton, W.S. 72, 73
 Fernyhough, C. 26
 first-episode schizophrenia 7, 8, 205–17
 acute agitation 212
 adherence, treatment 214–15
 antipsychotics 8, 210–12
 anxiety 215–16
 clinical assessment 206–10
 depression 215–16
 diagnosis 206–10, 207–9, 213–14
 extrapyramidal motor side-effects 210, 211
 family intervention 195, 212–13
 predictors of poor outcome 214
 psychosocial interventions 212–13
 Fisher, W. 106
 flattened affect 37
- flunitrazepam 137
 fluoxetine 13
 flupenthixol 4
 flupenthixol decanoate 14
 fluphenazine 4
 fluphenazine decanoate 14, 38–9
 fluspirilene 14
 fluvoxamine 13, 40
 Freeman, D. 28
 Frith, C. 49
- galactorrhea 187
 galantamine 40
 Ganesan, S. 117
 glutamatergic agents 15
 glycine 40
 Goff, D.C. 68, 82
 Goodwin, R. 67
 Gordon, J. 106
 Graham, H.L. 106
 group therapy 106
- CBT 31
 family intervention 195–6
 gynecomastia 187
- Hafner, J. 67, 68, 70
 hallucinations:
 behavioral interventions 24
 cognitive behavior therapy (CBT) 27
 ear plug use 26
 psychological approaches 24–27, 25
 and violence 132
- haloperidol 1, 2, 3, 4, 38, 39, 64
 acute arousal and agitation in psychosis 120
 acute behavioral disturbance 117, 118
 and delirium 112
 first-episode schizophrenia 210–11
 use with mirtazapine 13
- haloperidol decanoate 14
 Halperin, S. 70
 Harvey, P.D. 71
 health, general 81–93
 modifiable risk factors 84–8, 85
 prevention approaches 88–92
- Hearing Voices Network 27
 heroin 101
 HIV 102
 Hogarty, G.E. 54, 197
 homelessness 102
 homicide 129, 130
 hormonal therapies 181
 hormones: effect on symptoms 186
- Huppert, J.D. 68
 hyperglycemia 85, 87
 hypertension 85, 86
 hypodopaminergia 3
- in vivo amplified skills training (IVAST) 170–1, 171
 Independent Living Skills Inventory (ILSI) 230, 245
 Indianapolis Vocational Intervention Program 154–7, 156
 Individual Placement and Support (IPS) 151
 infectious disease 83
 insight 145, 214–15
 insomnia 19
 insulin resistance 87
 integrated psychological therapy 226
 intelligence quotient (IQ) 47, 48, 144
- James, W. 106
 Jones, S.R. 26
 Josiassen, R.C. 12
- Kane, J.M. 18
 Kasanin, J. 61
 Kavanagh, D. 104–5, 106
 Kemp, R. 147
 Kendlar, K.S. 68
 Kingdon, D.G. 147
 Kingsep, P. 70

- Klosterkotter, J. 206
 Kotler, M. 65
 Kottgen, C. 197
 Kraepelin, E. 47, 61
 Krystal, J.H. 107
 Kuipers, E. 30
 Kulkarni, J. 181
- Lambeth Early Onset (LEO) trial 217
 Leff, J.P. 196, 197
 legal factors 231
 Leucht, S. 7
 Levinson, D.F. 66–7
 levomepromazine (methotrimeprazine) 4
 Lewis, G. 48, 68
 Liberman, R.P. 167
 Lieberman, J.A. 210
 life skills 51, 55–6
 lifespan 81
 Likert scales 237, 246, 248, 250–1
 Linszen, D. 199
 lipid screening 90, 91
 lithium 8, 9
 in augmentation 13, 15
 first-episode schizophrenia 215
 reducing violence 137
 long-acting atypical antipsychotics 18
 long-stay institutions: negative symptoms 40–1
 longitudinal data collection 230–1
 lorazepam:
 acute agitation 212
 acute arousal and agitation in psychosis 120
 acute behavioral disturbance 117, 119
 and delirium 112
 loxapine 4
 LSD 101
 lung cancer 82
 Lysaker, P.H. 72
- MacArthur-Maudsley Delusions Assessment Schedule (MADS) 242, 249
 Mari, J.J. 195, 200–1
 Martlatt, G. 106
 McCreadie, R.G. 88–92
 McEvoy, J.P. 87
 McFarlane, W.R. 199
 McGlashan, T.H. 72, 73
 McGurk, S.R. 54, 161
 McKay, D. 73
 McKiernan, K. 73
 Meagher, D.J. 112
 medical screening 90–2, 91
 medication algorithms 8, 9, 224–5
 menopause 186–7
 menstrual irregularity 187
 metabolic effects: in women 187
 metabolic screening and monitoring form 90–2
 metabolic syndrome 87, 87–8
 metacognition 57
 methotrimeprazine 4
 Micro-Modules Learning Test (MMLT) 241, 246
- Miller, W. 106
 mirtazapine 13, 40
 mood stabilizers 13, 221
 Moriana, J.A. 70
 mortality 81–2
 medical causes 82–4
 modifiable risk factors 84–8, 85
 primary and secondary prevention 88–92
 motivational interviewing (MI) 228–9
 Mueser, K.T. 104, 105
 Mingyuan, Z. 198
 motivation: and work 153, 154
- naltrexone 107
 National Health and Nutrition Examination Survey (NHANES) III 82, 87–8
 negative symptoms 19
 diagnosis 36–7
 due to extrapyramidal side-effects (EPSE) 36
 and family 41–2
 management 35–42
 management of secondary 37–9
 treatment of primary 39–40
 nervous system diseases 82
 neuroleptic malignant syndrome (NMS) 18, 19, 117, 121
 Neurocognitive Enhancement Therapy (NET) 158–61
 neurocognitive impairment 225–6
 neuroleptics 187–8
 nicotine:
 in augmentation 15
 effects on cognition 53
 non-compliance 19
see also adherence, treatment
 novel antipsychotics *see* atypical antipsychotics
- obesity 84–6, 85, 90, 91
 obsessive-compulsive disorder 71, 72–4
 Observational Scale for Inpatient Evaluation (NOSIE) 230
 oculogyric crises 211
 olanzapine 2, 5, 6, 8, 9, 10
 acute arousal and agitation in psychosis 118, 120
 acute behavioral disturbance 117, 118
 and delirium 112
 depot form 18
 and depression 64, 65
 and dyslipidemia 86
 first-episode schizophrenia 210–11
 and insulin resistance 87
 and metabolic syndrome 88
 negative symptoms 38, 39
 obsessive compulsive symptoms 74
 social anxiety disorder 71
 treatment-resistant schizophrenia 224
 and weight gain 85, 86
 Ongur, D. 68
 osteoporosis 186, 187, 187

- paliperidone 3
- Pallanti, S. 69–71, 70
- paranoid delusions 28
- parenting 185–6
- parkinsonism 1, 2, 19, 63
 - in women 187
- patient education 89, 89
- Penn, D. 172
- Pennsylvania State Hospital System's Seclusion and Restraint Reduction Program 115, 115
- pergolide 40
- pericyazine 4
- perphenazine 4
- personal checklist: treatment adherence 148
- personality: and violence 133
- pharmacodynamic factors: treatment response 182
- pharmacological treatment 1–20
 - acute arousal and agitation in psychosis 120
 - acute behavioral disturbance 117–25
 - augmentation 12–13, 15
 - cognitive dysfunctions 52–3
 - depression 66
 - obsessive-compulsive disorder 74
 - reducing violence 137
 - social anxiety disorder 71
 - substance abuse 107
- pharmacotherapy: and psychological treatments 41
- pharmokinetic factors: treatment response 182
- phenothiazines 4, 184–5
- phenytoin 137
- physical examination 209–10
- physical restraint 115
- Pilling, S. 200
- pimozide 3, 4
- pipotiazine palmitate 14
- Pitschel-Walz, G. 196, 200
- Pokos, V. 68
- polypharmacy 229
- positive and negative syndrome scale (PANSS) 161
- positive symptoms 23–32
 - effects of cognitive difficulties on 49–50
 - effects of medication 23
 - and negative symptoms 6, 36
- Poyurovsky, M. 74
- pregnancy 184–5
- primary negative symptoms 36, 36, 39–40
- promazine 4
- pschoeducation programs 65–6
- pseudospecific response 37
- psychoeducation 41–2, 212–13
- psychological treatments 31–32
 - and cognitive dysfunctions 53–8
 - delusions 27–28
 - depression 65–6
 - directly changing cognition 53–4
 - environment 57–8
 - models 24
 - obsessive-compulsive disorder 73
 - psychological treatments (*Continued*)
 - and pharmacotherapy 41
 - positive symptoms 23–32
 - reducing violence 136–7
 - rehabilitation programs 57
- psychopathology: consequences of 132–3
- psychopharmacotherapy 229–31
- psychosis:
 - acute behavioral disturbance in 112
 - early episode treatment 7, 8
 - treatment of relapse 7, 9
- psychosocial treatments 55–6
 - first-episode schizophrenia 212–13
 - negative symptoms 40–1
 - treatment-resistant schizophrenia 223
 - women 183
- psychostimulant drugs: cognition 53
- pulmonary disease 84
- Putman, R. 169
- quality of life 66, 227
 - quality of life scale 154
- quetiapine 2, 6, 8, 9, 10, 38
 - acute behavioral disturbance 117, 119
 - antidepressant effects 64
 - use with clozapine 13
 - and delirium 112
 - and EPSE 36
 - first-episode schizophrenia 210–11
 - social anxiety disorder 71
 - treatment-resistant schizophrenia 224
 - and weight 85
- Randolph, E.T. 198
- rating scales 237–51
 - criteria for selection 238
 - needs and strengths 244–6
 - skills and deficits 246–7
 - specific mediators and moderators 247–51
 - symptoms 238–9, 244
- reactance 145
- rebound 17
- recovery concept 229
- Reeder, C. 54, 57
- refractory *see* treatment resistant
- rehabilitation 50–1, 230
- Reichenberg, A. 48
- relapse 7, 9, 214–15
- residential settings:
 - psychopharmacological assessment 229–31
 - treatment-resistant schizophrenia 227–8
- respiratory diseases 82
- Reznik, I. 74
- risk factors 205–6, 206
- risperidone 2, 5, 6, 8, 9, 10, 16
 - acute arousal and agitation in psychosis 118, 120
 - acute behavioral disturbance 117, 119
 - antidepressant effects 64
 - in augmentation 15
 - use with clozapine 12

- antidepressant effects (*Continued*)
 - and delirium 112
 - depot form 18
 - first-episode schizophrenia 210–11
 - and negative symptoms 38, 39
 - in pregnancy 185
 - reducing violence 137
 - side-effects 14
 - social anxiety disorder 71
 - treatment-resistant schizophrenia 223, 224
 - and weight gain 85, 86
 - Robinson, D. 214–15
 - Rollnick, S. 106
 - Romme, M. 27
 - Rosen, I. 72
- Satisfaction with Life Domains Scale (SLDS)
 - 243, 250–1
- schizoaffective disorder 61
- schizophrenia spectrum disorder (SDD) 48
- Schooler, N.R. 99, 210
- screening investigations 209
- seclusion 115–16
- debriefing form 116
- second generation drugs 38, 39–40, 211
- secondary negative symptoms 36, 36
- and antipsychotic drugs 38–9
- selective serotonin reuptake inhibitors (SSRIs)
 - 13, 67, 74, 216
- self efficacy 54
- Self-Esteem Rating Scale-Short Form (SERS-SF)
 - 242, 248
- 'self-medication' 103, 107, 107
- self-monitoring 147, 148
- and voices 25, 50
- Sensky, T. 30
- serotonergic antidepressants 74, 137
- serotonin 2, 181
- serotonin receptors 107
- serotonin reuptake inhibitors (SSRIs) 13
- sertindole 2, 5, 6, 9
- Service Engagement Scale (SES) 241, 247–8
- sexuality 183–4, 187
- side-effects:
 - and adherence 144
 - anticholinergic drugs 39
 - antipsychotics 18
 - atypical antipsychotics 5, 6
 - clozapine 1–2, 10, 12
 - in combination treatments 12
 - depot antipsychotics 14
 - negative symptoms 36
 - therapeutic interventions 107
 - typical antipsychotics 3, 4, 5
- Simpson, G.M. 18
- Siris, S.G. 62, 64, 66
- Slade, P.D. 24
- Smith, T.E. 68
- smoking 84, 85, 88, 99
- social anxiety disorder 69–71
- social cognition 173
- social context: violence 133
- Social Functioning Scale (SFS) 241, 246–7
- social interventions: reducing violence 136
- social skills:
 - classification 167
 - in the community 168–74
 - and work 153, 157–8
- social skills training 70, 166–74, 173
- development 166–8
- efficacy 168
- treatment-resistant schizophrenia 226
- socialization:
 - barriers to 170
 - enhancing 165–74
- sodium valproate 8, 9
- in augmentation 13, 15
- first-episode schizophrenia 211
- Spaulding, W. 54, 226
- Spencer, C. 100, 103, 106
- SSRIs 13, 67, 74, 216
- Stahl, S.M. 5
- standardized mortality ratios 81–2, 82
- Stengel, E. 72
- stigma: and adherence 145–6
- stimulants: in augmentation 15
- Streiner, D.L. 195, 200–1
- substance abuse 19, 88, 99–108
- clinical implications 102, 102
- impact on schizophrenia 101
- family intervention 195
- first-episode schizophrenia 213
- motivations for 103, 103–4
- pharmacological strategies 107, 107
- prevalence 99–101, 100
- psychosocial treatments 105, 105–6
- treatment-resistant schizophrenia 228
- treatments 104–5
- and violence 102, 130–1, 137–8
- substituted benzamides 4
- suicide 63
- sulpiride 4
- antidepressant effects 65
- use with clozapine 12
- supported employment (SE) 151
- symptoms:
 - early 205–6
 - effect of estrogen on 180–2
 - effects of cognitive difficulties on 49–50
 - as mediators of violence 131–2
 - negative 35–42
 - rating scales 238–9, 244
 - treatment resistance 10, 222
 - women 179–80
- tardive dyskinesia (TD) 1, 2, 7, 10, 19, 188
- and estrogen 182
- in women 187
- Tarrier, N. 30, 196, 197, 200
- Tauber, R. 157, 158, 170
- TD *see* tardive dyskinesia (TD)
- Tengström, A. 130–1

- therapeutic goals: reducing violence 138
 therapeutic jurisprudence (TJ) 231
 therapeutic relationships 183
 Thinking Skills for Work 161
 thioridazine 3, 4
 thioxanthines 4
 Time Line Follow-Back Calendar (TLFBC) 242, 248–9
 Time-Sample Behavioral Checklist (TSBC) 230
 token economies 227
 Tollefson, G.D. 64, 66
 topiramate 137
 tranquilizers 101
 treatment algorithms 8, 9
 treatment-resistant schizophrenia 1, 10, 12, 221–3
 augmentation strategies 12, 12–13, 14, 15
 cognitive behavioral therapy 228–9
 contingency management 227
 environmental engineering 226–7
 medication algorithms 224–5
 neuropsychological therapy 225–6
 risk assessment and management 232
 therapeutic jurisprudence (TJ) 231
 tools 224
 tricyclics 13
 trifluoperazine 4
 Trower, P. 31
 Turkington, D. 147
 Turpin, G. 194
 typical antipsychotics 1, 3, 4, 5, 7, 8
 acute agitation 212
 acute behavioral disturbance 117, 118
 changing to atypicals 15–16
 and cognitive dysfunctions 52
 depot medication 12
 early episode psychosis treatment 7
 and ‘self medication’ 107
 side-effects 3, 4, 5, 18
 treatment-resistant schizophrenia 221–2, 225
 use with atypical agents 12
 see also specific drugs
 UCLA Social and Independent Living Skills Program 167–8
 unemployment, effect of 133
 Valmaggia, L.R. 30
 valproate: reducing violence 137
 Velligan, D.I. 54
 Vevera, J. 130
 violent behavior 129–39
 mediators of 130–3, 131, 134
 two type model 132, 132
 interventions 139
 management principles 135–6
 measures to reduce 134–8, 139
 risk assessment 135, 135
 substance abuse and 102, 130–1, 137–8
 Vocational Cognitive Rating Scale (VCRS) 159–60
 voices:
 and anxiety 24, 26
 normalization 27
 psychological interventions 24–27, 25
 self monitoring 49–50, 50
 Wallace, C.J. 157, 158
 weight gain 188
 behavioral therapy 91
 in women 187, 187–8
 women: clinical needs 179–98
 adverse treatment effects 187–8
 age at onset 179–80
 cognition 180–2
 comorbidities 180
 diagnosis 179, 180
 estrogen 180–2, 181
 long term outcome 183
 menopause 186–7
 pregnancy 184–5, 185
 presentations 180
 psychosocial treatments 183
 response to antipsychotic treatment 182
 sexuality 183–4
 work 151–62
 behavior feedback groups 152–4
 Indianapolis Vocational Intervention Program 154–7
 interventions 152
 Neurocognitive Enhancement Therapy (NET) 158–61
 supported employment (SE) 151
 workplace fundamental skills module 157–8
 Work Behavior Inventory (WBI) 152–4, 153, 241, 247
 Working Alliance Inventory (WAI) 243, 250
 workplace fundamental skills module 157, 157–8
 Wright, P. 118
 Wykes, T. 31, 54, 57
 Xiong, W. 198
 young adults 216–17
 Yung, A.R. 206
 Zastowny, R.R. 198
 Zeidonis, D. 106
 Zhang, M. 198
 ziprasidone 2, 5, 6, 8, 9, 38
 acute arousal 118
 acute behavioral disturbance 117, 118, 119
 antidepressant effects 64
 and dyslipidemia 86
 and insulin resistance 87
 treatment-resistant schizophrenia 224
 and weight 85, 86
 zotepine 2, 6
 zuclopenthixol (Clopixol Acuphase) 4, 121–3
 acute behavioral disturbances 119, 120
 guidelines 123, 124–5
 zuclopenthixol acetate 212
 zuclopenthixol decanoate 14

Pharmacological and Psychosocial Treatments in Schizophrenia

SECOND EDITION



"A book that aims to give a succinct overview of the holistic treatment of schizophrenia is extremely welcome... I am happy to recommend it to mental health practitioners as a guide to psychosocial treatments"

Journal of Mental Health

The new edition of *Pharmacological and Psychosocial Treatments in Schizophrenia* provides an authoritative review of pharmacological and psychosocial treatment interventions for individuals with schizophrenia and related disorders. The text has been fully updated, revised, expanded and new chapters encompass co-morbid general health issues, violence in schizophrenia, the special needs of women with schizophrenia, first-episode psychosis, treatment-resistant schizophrenia, and clinical rating scales in schizophrenia.

Each topic is covered with a review of the relevant literature, a summary of the main findings and some tips about how to meet these needs in clinical practice. Thus, the book is both a review and a resource for clinicians and service-providers.

The principal Editors and their contributors give an opportunity for leading international experts in the field to contribute and provide an international flavor to the text.

Edited by

David J Castle MSc DLSHTM MD MRCPsych FRANZCP, Chair of Psychiatry, St Vincent's Health and The University of Melbourne, Fitzroy, Victoria, Australia

David L Copolov PhD FRACP FRANZCP, Professor of Psychiatry, Monash University, Clayton, Victoria, Australia

Til Wykes MPhil PhD Professor and Head, Centre for Recovery in Severe Psychosis, Institute of Psychiatry, London, UK

Kim T Mueser PhD Professor of Psychiatry, Dartmouth Medical School Hanover, NH, USA

informa

healthcare

www.informahhealthcare.com

